Lecture Given by Dr. Pierre Kory January 27, 2021 on a Webinar Hosted by YPO Gold’s Southern California Chapter for Hundreds of CEOs Within the Network Internationally

Video of the Live Webinar Also Available

Lecturer: Dr. Pierre Kory
Internationally Recognized Pulmonary & Critical Care Specialist
President, Frontline COVID-19 Critical Care Alliance

Host: YPO Gold Southern California Chapter – Internationally Distributed

Event Chair: Jeff Hanson
YPO Gold Southern California Chapter, member
American Healthcare Investors, Co-Founder
FLCCC Alliance, Board Member

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A Review of the Evidence Base Demonstrating the Efficacy of Ivermectin in the Prevention & Treatment of COVID-19

Pierre Kory, MD, MPA
President, Front Line Covid-19 Critical Care Alliance
www.flccc.net
Agenda

Section I: FLCCC Alliance Introduction & High-Level Summary of Recent Critical Events

Section II: What Is Ivermectin?

Section III: Review of the International Trials Data Demonstrating Efficacy
- Effective Pre-Exposure Preventative
- Effective Post-Exposure Preventative
- Effective Treatment Across All Stages of the Disease
- Effective in “Long-Haul” COVID-19 Syndrome

Section IV: Overview of Select U.S. Hospitals & Other Providers Using Ivermectin & N.I.H. Discussion

Section V: Conclusions & Call to Action

Section VI: Addendum of Deeper Scientific Data
Section I

Introduction to FLCCC Alliance & High-Level Summary of Recent Critical Events
Introduction: The FLCCC Alliance

Paul E. Marik, M.D., FCCM, FCCP
- Endowed Professor of Medicine
- Chief, Div. of Pulmonary & Critical Care Medicine
- Eastern Virginia Medical School Norfolk, Virginia

Pierre Kory, M.D., M.P.A.
- Pulmonary and Critical Care Specialist
- President, Frontline COVID-19 Critical Care Alliance (FLCCC Alliance)

G. Umberto Meduri, M.D.
- Professor of Medicine
- University of Tennessee Health Science Center
- Pulmonary, Critical Care & Sleep Medicine and Research Services
- Memphis V.A. Medical Center

Joseph Varon, M.D., FCCP, FCCM
- Professor of Acute & Continuing Care
- Chief of Staff & Chief of Critical Care
- United Memorial Medical Center, Houston, Texas

Jose Iglesias, D.O.
- Assoc. Prof., Hackensack Meridian School of Medicine at Seton Hall
- Dept. of Nephrology & Critical Care / Community Medical Center
- Dept. of Nephrology, Jersey Shore University Medical Center
- Neptune, New Jersey

Founding members

Keith Berkowitz, M.D., M.B.A.
- Medical Director, Center for Balanced Health
- Voluntary Attending Physician, Lenox Hill Hosp, New York, New York

Howard Kornfeld, M.D.
- President, Pharmacology Policy Institute
- Clinical Faculty, Pain Fellowship Program,
  Univ. of California, San Francisco (UCSF) School of Medicine
- Founder & Medical Director, Recovery Without Walls
  Mill Valley, California

Fred Wagshal, M.D.
- Pulmonologist & Med. Dir., Lung Center of America
- Clinical Instructor, Wright State University School of Medicine,
  Dayton, Ohio

Clinical advisors

Scott Mitchell, MRCS
- Associate Specialist
- Emergency Department
- Princess Elizabeth Hospital
- States of Guernsey

Eivind H. Vinjevoll, M.D.
- Senior Consultant Anesthesiologist
- Intensive Care, Emergency Medicine, Anesthesia
- Volda, Norway
Introduction & Timeline of Critical Recent Events

Who Are We?
- Formed in March 2020 by Dr. Paul Marik; second most published intensivist in history, globally
- Five of some of the most highly published and internationally recognized ICU physicians in the world
- All professors of medicine, research scientists, and top ICU doctors at leading U.S. medical schools
- Nearly 2,000 peer-reviewed papers
- Over 100 years of bedside ICU experience and near-daily care of COVID-19 patients since the beginning

May 7, 2020: First Testimony Before U.S. Senate Subcommittee
- Testified that corticosteroids are essential in the treatment of late-stage hospitalized COVID-19 patients
- Summarily dismissed thereafter by the global healthcare community; even mocked and ridiculed
- Dr. Umberto Meduri is one of the five founders of FLCCC Alliance; undisputed global expert in corticosteroids, ARDS, and non-invasive ventilation

June 16, 2020: The Oxford RECOVERY Trial Results are Published
- Within five weeks of my testimony, the Oxford RECOVERY Trial confirmed that the FLCCC Alliance was right
- Overnight corticosteroids immediately became global standard for treating this category of patient
- P.S. -- Nobody called to apologize…
Timeline of Critical Recent Events (Cont’d.)

Early October 2020: The FLCCC Alliance Continued Pouring Through International Trials Data

- Team continuously reviewed all emerging trials data
- Identified a “data signal” – small series of profound trial results
- Began writing a manuscript summarizing 27 studies across 18 countries
- Passed peer-review mid-January and will be published by a high-impact U.S. medical journal imminently
- Four peer-reviewers; two were FDA-employed scientists and one an N.I.H.-employed scientist
- Link to Final Manuscript: https://osf.io/wx3zn/

Late November 2020: The W.H.O. Consultant Turns Attention to Ivermectin for COVID-19

- Dr. Andrew Hill, University of Liverpool, UK & renowned medical researcher
- Engaged by the W.H.O. in June 2020 to investigate existing drugs for off-label use for COVID-19
- His team conducted deep-dives into a number of potential drugs, all of which were ultimately failing the test
- In late November his team terminated their review of the other drugs, and turned their exclusive focus to ivermectin
- Conducted meta-analysis on numerous ivermectin RCTs internationally
- He initiated significant collaboration with the FLCCC Alliance in early December given our head-start in studying global trials data on the drug
Timeline of Critical Recent Events (Cont’d.)

December 8, 2020: Second Testimony Before U.S. Senate Subcommittee
- Testified that ivermectin is essential in the prevention and treatment COVID-19
- “We were right regarding corticosteroids in our testimony before this body last May, and we’re right again today regarding ivermectin.”
- Delivered passionate appeal to the N.I.H. to simply review the mountains of trials data available internationally

January 6, 2021: The N.I.H. Hears Presentation from Dr. Hill & The FLCCC Alliance
- N.I.H. contacted the FLCCC shortly after this second testimony and requested a joint presentation
- Dr. Andrew Hill and Drs. Marik and Kory present to the N.I.H.’s 22-person COVID-19 Treatment Panel
- I pleaded, “please take your foot off of the neck of ivermectin by upgrading your recommendation”
- Longstanding and inappropriate recommendation; inhibited use by physicians and hospitals
- Unshackle U.S. healthcare providers in the midst of a surge in the pandemic that is overwhelming hospitals
Timeline of Critical Recent Events (Cont’d.)

January 14, 2021: The N.I.H. Announces a Change in Its Position on Ivermectin

- Seven days after the joint presentation, the N.I.H. announced a significant upgrade in their position on ivermectin from “IIIA Against” to essentially “neutral, pending more trials data.”
- This is simultaneously “good” and “not enough.”
- Core take-away: it frees hospital systems, physicians, and others to introduce ivermectin into protocol and write scripts
- Further and immediate movement by the N.I.H. is essential
- Link to FLCCC Alliance’s Open Letter to the N.I.H.: https://tinyurl.com/yxu87m5s

January 18, 2021: Dr. Andrew Hill, Consultant to the W.H.O., Releases His Meta-Data

- The data from 17 randomized controlled trials internationally clearly indicates ‘statistically significant’ results across the board:
  - 75% reduction in mortality
  - Lower rates of hospitalization
  - Shorter duration of hospitalization
  - Higher rates of clinical recovery
  - Faster time to viral clearance

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  - Higher rates of clinical recovery
  - Faster time to viral clearance
Timeline of Critical Recent Events (Cont’d.)

January 23, 2021: The University of Oxford Announces plans for the PRINCIPLE Trial on ivermectin
- Nationwide U.K. trial to test ivermectin broadly as an early treatment option against COVID-19
- On January 24th, the FLCCC Alliance wrote an open letter to Oxford

January 27, 2021: Presentation to Member of the Biden COVID-19 Task Force
Contacted last week by a member of President Biden’s COVID-19 Task Force and asked to present our findings on ivermectin
Section II

What is Ivermectin?
What is Ivermectin?

- Well known, highly effective anti parasite medication
- Discoverers awarded Nobel Prize in 2015 for the drug’s impact on global health
- On the World Health Organization’s “Essential Medicines” list, FDA approved for decades
- ~3.7 billion doses distributed globally to-date; ~1 million doses distributed on a daily basis throughout the world (human use)
- Over 50% of the population of sub-Saharan Africa takes ivermectin on a regular basis
- Exceedingly strong safety profile; as of 2016, only 1,668 adverse event reports had been received by the W.H.O.’s international drug monitoring system (VigiBase)
What is Ivermectin?

Representative highlights from our peer-reviewed manuscript -- Link to Final Manuscript: https://osf.io/wx3zn/

- Since 2012, multiple *in vitro* studies find that Ivermectin inhibits many viruses, including Zika, Dengue, West Nile, Influenza and others

- Inhibits SARS-CoV-2 replication and binding to host tissue via several observed and proposed mechanisms

- Recently found to have potent anti-inflammatory properties with profound inhibition of multiple inflammatory mediators

- Significantly diminishes viral load and protects against organ damage in animal models when infected with SARS-CoV-2

- Clinical trials results in past 6 months of the pandemic have shown that in humans, ivermectin:
  - Prevents transmission and development of COVID-19 disease in those exposed to infected patients
  - Hastens recovery and prevents deterioration in patients with mild to moderate disease treated early after symptom onset
  - Hastens recovery and avoidance of ICU admission and death in hospitalized patients
  - Reduces mortality in critically ill patients with COVID-19
  - Leads to striking reductions in case-fatality rates in regions with widespread use
Section III

Review of the Existing International Clinical Trials Data
Existing Clinical Trials Evidence-Base

- 32 controlled trials including over 6,500 patients

- 20 studies are randomized, controlled trials (17 treatment, 3 prophylaxis/preventative) and include over 2,800 patients
  - 6 double-blind studies, 1 single blind
    - 5 of the 20 randomized controlled trials (RTCs) are unpublished – but results known to the W.H.O.
  - 12 studies are observational, controlled trials, matched comparison groups
  - 12 of the 32 controlled trials have been published in peer-reviewed journals

- Unitaid/W.H.O ACT Accelerator Program consultant - Dr. Andrew Hill, Senior Research Fellow at University of Liverpool, U.K.
  - Conducting a systematic review of only RCT’s and only on treatment of COVID-19 (not studying prophylaxis/prevention – yet)
  - 59 active trials registered, has results from 17 “randomized, controlled, treatment” trials which include over 2,100 patients
Ongoing Randomized Clinical Trials

56 trials
n=7491
## Prophylaxis (Preventative) Trials Data

<table>
<thead>
<tr>
<th>Author, Country, Source</th>
<th>Study Design, Size</th>
<th>Study Subjects</th>
<th>Ivermectin Dose</th>
<th>Dose Frequency</th>
<th>Clinical Outcomes Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shouman W, Egypt, <a href="http://www.clinicaltrials.gov">www.clinicaltrials.gov</a></td>
<td>RCT N=440</td>
<td>Household members of pts with COVID-19 PCR test</td>
<td>40–60kg: 15mg, ≥ 60kg: 18mg</td>
<td>Two doses, every 72 hours apart</td>
<td>7.4% vs. 58.4% developed COVID-19 symptoms, p &lt; .001</td>
</tr>
<tr>
<td>Elpazzer A, Egypt ResearchSquare, doi:10.21203/rs.3.rs-100956/v1</td>
<td>RCT N=200</td>
<td>Health care and household contacts of pts with COVID-19 PCR test</td>
<td>0.4mg/kg</td>
<td>Two doses, Day 1 and Day 7</td>
<td>2% vs. 10% tested positive for COVID-19, p &lt; .05</td>
</tr>
<tr>
<td>Chala R, Argentina, NCT04071710, Clinicaltrials.gov</td>
<td>RCT N=234</td>
<td>Health care Workers</td>
<td>12mg</td>
<td>Every 7 days</td>
<td>3.4% vs. 21.4%, p = .0001</td>
</tr>
<tr>
<td>Carvalho H, Argentina, Journal of Biochemical Research and Investigation, doi:10.31546/6333-8565.1007</td>
<td>OCT N=229</td>
<td>Healthy patients negative for COVID-19 PCR</td>
<td>0.2mg drops a day x 28 days</td>
<td>1 drop five times a day x 28 days</td>
<td>0.0% vs. 11.2% contracted COVID-19, p &lt; .001</td>
</tr>
<tr>
<td>Alam MT, Bangladesh, European J Med Hlth Sciences, 10.24018/ejmed.2020.2.6.599, OCT N=118</td>
<td>Health care Workers</td>
<td>12mg</td>
<td>Monthly</td>
<td>6.9% vs. 73.3%, p = .0</td>
<td></td>
</tr>
<tr>
<td>Carvalho H, Argentina, Journal of Biochemical Research and Investigation, doi:10.31546/6333-8565.1007</td>
<td>OCT N=193</td>
<td>Health care Workers</td>
<td>12 mg</td>
<td>Once weekly for up to ten weeks</td>
<td>0.0% of the 788 workers taking ivermectin vs. 58% of the 407 controls contracted COVID-19</td>
</tr>
<tr>
<td>Behera P, India, medRxiv, doi:10.1101/2020.10.29.20222661</td>
<td>OCT N=186 case control pairs</td>
<td>Health care Workers</td>
<td>0.3 mg/kg</td>
<td>Day 1 and Day 4</td>
<td>2 doses reduced odds of contracting COVID-19 (OR 0.27, 95% CI 0.16–0.53)</td>
</tr>
<tr>
<td>Bernardin C, France, Annales de Dermatologie et de Venereologie, doi:10.1016/j.annder.2020.09.2031</td>
<td>OCT N=69 case control pairs</td>
<td>Nursing home Residents</td>
<td>0.2 mg/kg</td>
<td>Once</td>
<td>10.1% vs. 22.6% residents contracted COVID-19, 0.0% vs. 4.9% mortality</td>
</tr>
</tbody>
</table>

- Three randomized controlled trials (RCTs) with 774 patients
- Five observational controlled trials (OCTs) with 2,052 patients
Meta-Analysis of Ivermectin Prophylaxis/Preventative Studies

Note: Meta-Analysis of randomized controlled trials is the highest form of evidence in medical research
Mild-Moderate Illness Trials

- Six RCTs with 742 patients, significant reductions in:
  - Time to viral clearance
  - Time to clinical recovery
  - Rates of hospitalization
  - Rates of deterioration
  - Mortality (one trial)

- Four case-series with 3,394 patients
  - High rates of recovery
  - Low/no rates of hospitalizations

<table>
<thead>
<tr>
<th>Clinical Trials – Outpatients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AUTHOR, COUNTRY, SOURCE</strong></td>
</tr>
<tr>
<td><strong>STUDY DESIGN/ SIZE</strong></td>
</tr>
<tr>
<td><strong>STUDY SUBJECTS</strong></td>
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<tr>
<td><strong>IVERMECTIN DOSE</strong></td>
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<tr>
<td><strong>DOSE FREQUENCY</strong></td>
</tr>
<tr>
<td><strong>CLINICAL OUTCOMES REPORTED</strong></td>
</tr>
<tr>
<td>Mahmodul R, Bangladesh <a href="http://www.clinicaltrials.gov">www.clinicaltrials.gov</a> NCT0452183 DB-RCT N=363 Outpatients and hospitalized 12mg + doxycycline Once, within 3 days of PCR+ test Early improvement 60.7% vs. 44.5%, p&lt;.03, deterioration 8.7% vs 17.8%, p&lt;.02</td>
</tr>
<tr>
<td>Chowdhury A, Bangladesh Research Square doi.org/10.21203.rs.3.x.38896/v1 DB-RCT N=116 Outpatients 0.2 mg/kg + doxycycline Once Recovery time 5.9 vs 9.3 days (p&lt;.07)</td>
</tr>
<tr>
<td>Ravikant, India medRxiv doi.org/10.1101/2020.05.21249930 DB-RCT N=115 Mild-moderate illness 12mg Daily for 2 days No diff in day 6 PCR+ 0% vs 6.9% mortality, p=0.19</td>
</tr>
<tr>
<td>Babalola OJ, Nigeria medRxiv doi.org/10.1101/2020.05.21249931 DB-RCT N=62 Mild-moderate illness 6mg and 12 mg Every 48h x 2 weeks Time to viral clearance: 4.6 days high dose vs 6.0 vs low dose vs 9.1 days control (p=0.06)</td>
</tr>
<tr>
<td>Poddar CS, Bangladesh IMC J Med Sci 2020;14(2) RCT N=62 Outpatients 0.2 mg/kg Once Recovery time 10.1 vs 11.3 days (NS), average time 3.3 vs 6.3 (NS)</td>
</tr>
<tr>
<td>Chacona C, Spain Research Square doi.org/10.21203.rs.3.x.116547/v1 RCT N=24 Outpatients 0.4mg/kg Once No diff in PCR+ Day 7, lower viral load days 4 and 7, (p&lt;0.05), 76 vs 158 pg, days of fever (p&lt;0.05), 68 vs 98 pg, days of cough (p&lt;0.05)</td>
</tr>
<tr>
<td>Morgenstern J, Dominican Republic medRxiv doi.org/10.1101/2020.10.29.20222505 Case Series N=3,009 Outpatients and hospitalized Outpatients: 0.4mg/kg Hospital Patients: 0.3mg/kg Outpatients:0.3mg/kg x 1 dose Hospital: 0.3mg/kg Days 1,2,6,7 Mortality ≤ 0.03% in 2888 outpatients, 1% in 300 non-ICU hospital patients, 30.6% in 111 ICU patients</td>
</tr>
<tr>
<td>Corella H, Argentina medRxiv doi.org/10.1101/2020.09.10.20191619 Case Series N=167 Outpatients and hospitalized 24mg=mild, 36mg=moderate, 48mg=severe Days 0 and 7 All 135 with mild illness survived, 1/32 (3.1%) of hospitalized patients died</td>
</tr>
<tr>
<td>Alam A, Bangladesh, J of Bangladesh College Phys and Surg, 2020;38:10-15 doi.org/10.3329/jbpc.v38i01.47512 Case series N=100 Outpatients 0.2 mg/kg + doxycycline Once All improved within 72 hours</td>
</tr>
<tr>
<td>Espitia-Hernandez G, Mexico Biomedical Research <a href="http://www.biomedres.info/biomedr...proof-.pdf">www.biomedres.info/biomedr...proof-.pdf</a> <a href="http://www.clinicaltrials.gov">www.clinicaltrials.gov</a> N=28 Outpatients 6mg Days 1,2, 7, 8 All pts recovered Average recovery time 3.6 days</td>
</tr>
</tbody>
</table>
# Effects of Ivermectin on viral clearance in randomized trials – multi-day dosing

<table>
<thead>
<tr>
<th>Study</th>
<th>Country (n)</th>
<th>Daily dose</th>
<th>Duration</th>
<th>Viral load endpoint</th>
<th>Result IVA vs Control</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elgazzar et al</td>
<td>Egypt, n=200</td>
<td>0.4 mg/kg</td>
<td>5 days (OL)</td>
<td>Days detectable</td>
<td>5 vs 10 days</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Mild / moderate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Elgazzar et al</td>
<td>Egypt, n=200</td>
<td>0.4 mg/kg</td>
<td>5 days (OL)</td>
<td>Days detectable</td>
<td>6 vs 12 days</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Severe</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Okomus et al</td>
<td>Turkey, n=60</td>
<td>0.2 mg/kg</td>
<td>5 days (DB)</td>
<td>Day 10 PCR Neg</td>
<td>88% vs 38%</td>
<td>p = 0.01</td>
</tr>
<tr>
<td>Garrahan et al</td>
<td>Argentina, n=45</td>
<td>0.6 mg/kg</td>
<td>5 days</td>
<td>PK/PD</td>
<td>Dose-related</td>
<td>p = 0.02</td>
</tr>
<tr>
<td>Babaloa et al *</td>
<td>Nigeria, n=60</td>
<td>0.1-0.2 mg/kg</td>
<td>2 / week (DB)</td>
<td>Time to PCR neg</td>
<td>2 x faster clearance</td>
<td>p = 0.003</td>
</tr>
<tr>
<td>Ahmed et al *</td>
<td>Bangladesh, n=72</td>
<td>0.2 mg/kg</td>
<td>5 days (DB)</td>
<td>Time to PCR neg</td>
<td>7 vs 14 days</td>
<td>p = 0.005</td>
</tr>
</tbody>
</table>

* dose-response effects seen
Could it work in Hospitalized Patients and why?

- Viral replication is either severely diminished or absent by the time patients enter the hospital.

It is the non-viable RNA fragments of SARS-CoV-2 that provoke an overwhelming and injurious inflammatory response.
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Patients</th>
<th>Treatment</th>
<th>Dosing</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elgazzar A, Egypt ResearchSquare</td>
<td>RCT</td>
<td>N=400</td>
<td>Hospitalized Patients</td>
<td>0.4 mg/kg</td>
<td>Once</td>
</tr>
<tr>
<td>Niaee S. M. Research Square</td>
<td>RCT</td>
<td>N=180</td>
<td>Hospitalized Patients</td>
<td>0.2, 0.3, 0.4 mg/kg (3 dosing strategies)</td>
<td>Once vs. Days 1,3,5</td>
</tr>
<tr>
<td>Hashim H, Iraq medRiv</td>
<td>RCT</td>
<td>N=140</td>
<td>2/3 outpatients, 1/3 hospital pts</td>
<td>0.2 mg/kg + doxycycline</td>
<td>Daily for 2–3 days</td>
</tr>
<tr>
<td>Spoorithi S, India AIAM, 2020, 7(10):177-182</td>
<td>RCT</td>
<td>N=100</td>
<td>Hospitalized Patients</td>
<td>0.2mg/kg+ Doxycycline</td>
<td>Once</td>
</tr>
<tr>
<td>Ahmed S. Dhaka, Bangladesh International Journal of Infectious Disease</td>
<td>RCT</td>
<td>N=72</td>
<td>Hospitalized Patients</td>
<td>12mg</td>
<td>Daily for 5 days</td>
</tr>
<tr>
<td>Chachar AZK, Pakistan Int J Sciences</td>
<td>RCT</td>
<td>N=50</td>
<td>Hospitalized Patients-Mild</td>
<td>12mg</td>
<td>Two doses Day 1, one dose Day 2</td>
</tr>
<tr>
<td>Portman-Baracco A, Brazil Arch Bronconeumol. 2020</td>
<td>OCT</td>
<td>N=1408</td>
<td>Hospitalized patients</td>
<td>0.15 mg/kg</td>
<td>Once</td>
</tr>
<tr>
<td>Soto-Beccerra P, Peru medRiv</td>
<td>OCT</td>
<td>N=5683, IVN, N=563</td>
<td>Hospitalized patients, database analysis</td>
<td>Unknown dose &lt;48hrs after admission</td>
<td>Unknown</td>
</tr>
<tr>
<td>Rajter JC, Florida Chest 2020</td>
<td>OCT</td>
<td>N=280</td>
<td>Hospitalized patients</td>
<td>0.2 mg/kg + azithromycin</td>
<td>Day 1 and Day 7 if needed</td>
</tr>
<tr>
<td>Khan X, Bangladesh Arch Bronconeumol. 2020</td>
<td>OCT</td>
<td>N=248</td>
<td>Hospitalized patients</td>
<td>12 mg</td>
<td>Once on admission</td>
</tr>
<tr>
<td>Gortai F, Iraq medRiv</td>
<td>OCT</td>
<td>N=87</td>
<td>Hospitalized patients</td>
<td>0.2 mg/kg + HCQ and azithromycin</td>
<td>Once on admission</td>
</tr>
<tr>
<td>Campubli D. Spain Plos One</td>
<td>OCT</td>
<td>N=26</td>
<td>Hospitalized Patients</td>
<td>0.2mg/kg</td>
<td>Once, median of 12 days after symptom onset (8-18 days)</td>
</tr>
<tr>
<td>Bhudiraja S, India medRiv</td>
<td>Case Series</td>
<td>N=34</td>
<td>Hospitalized Patients</td>
<td>n/a</td>
<td>n/a</td>
</tr>
</tbody>
</table>

- Six randomized controlled trials (RCTs) with 952 patients
- Five observational controlled trials (OCTs) with 2,612 patients
- 6 controlled trials with statistically significant reductions in mortality
Meta-Analysis - Time to Clinical Recovery or LOS
Meta-Analysis of Mortality in COVID-19

<table>
<thead>
<tr>
<th>Group by RCT-Obs</th>
<th>Study name</th>
<th>Odds ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Z-Value</th>
<th>p-Value</th>
<th>Ivermectin</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>OBS</td>
<td>Rajter</td>
<td>0.524</td>
<td>0.287</td>
<td>0.958</td>
<td>-2.099</td>
<td>0.036</td>
<td>26 / 173</td>
<td>27 / 107</td>
</tr>
<tr>
<td>OBS</td>
<td>Khan</td>
<td>0.121</td>
<td>0.015</td>
<td>0.969</td>
<td>-1.990</td>
<td>0.047</td>
<td>1 / 115</td>
<td>2 / 133</td>
</tr>
<tr>
<td>OBS</td>
<td>Goyal</td>
<td>0.842</td>
<td>0.039</td>
<td>18.393</td>
<td>-0.109</td>
<td>0.913</td>
<td>0 / 16</td>
<td>2 / 71</td>
</tr>
<tr>
<td>OBS</td>
<td>Budhiraja</td>
<td>0.118</td>
<td>0.007</td>
<td>1.932</td>
<td>-1.499</td>
<td>0.134</td>
<td>0 / 34</td>
<td>103 / 942</td>
</tr>
<tr>
<td>OBS</td>
<td></td>
<td>0.451</td>
<td>0.250</td>
<td>0.789</td>
<td>-2.793</td>
<td>0.005</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCT</td>
<td>Mahmud</td>
<td>0.138</td>
<td>0.007</td>
<td>2.694</td>
<td>-1.306</td>
<td>0.192</td>
<td>0 / 183</td>
<td>3 / 180</td>
</tr>
<tr>
<td>RCT</td>
<td>Hashim</td>
<td>0.314</td>
<td>0.061</td>
<td>1.611</td>
<td>-1.389</td>
<td>0.165</td>
<td>2 / 70</td>
<td>6 / 70</td>
</tr>
<tr>
<td>RCT</td>
<td>Elgazzar</td>
<td>0.074</td>
<td>0.017</td>
<td>0.318</td>
<td>-3.502</td>
<td>0.000</td>
<td>2 / 200</td>
<td>24 / 200</td>
</tr>
<tr>
<td>RCT</td>
<td>Niaee</td>
<td>0.154</td>
<td>0.047</td>
<td>0.506</td>
<td>-3.080</td>
<td>0.002</td>
<td>4 / 120</td>
<td>11 / 60</td>
</tr>
<tr>
<td>RCT</td>
<td>Cadegiani</td>
<td>0.046</td>
<td>0.002</td>
<td>0.970</td>
<td>-1.980</td>
<td>0.048</td>
<td>0 / 585</td>
<td>2 / 137</td>
</tr>
<tr>
<td>RCT</td>
<td>Ravikulti</td>
<td>0.107</td>
<td>0.008</td>
<td>2.038</td>
<td>-1.488</td>
<td>0.137</td>
<td>0 / 55</td>
<td>4 / 57</td>
</tr>
<tr>
<td>RCT</td>
<td>Overall</td>
<td>0.134</td>
<td>0.065</td>
<td>0.777</td>
<td>-5.413</td>
<td>0.000</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Odds ratio and 95% CI

Favours Ivermectin  Favours Control

FRONT LINE COVID-19 CRITICAL CARE ALLIANCE - FLCCC.NET
PREVENTION & TREATMENT PROTOCOLS FOR COVID-19
“Long-Hauler” COVID-19 Syndrome

- High frequency of a constellation of persistent symptoms post-acute illness
  - Fatigue, aches, palpitations, rash, dizziness, headaches, poor concentration
  - Similar post-viral syndromes associated with Epstein-Barr and others
  - Often an absence of “objective findings” – frustrating for patient/physician/family

- Does Ivermectin have a role in these prolonged phases?
  - Encouraging reports from case series and increasing anecdotes
  - Aguirre-Chang, Peru: 33 patients with symptoms present > 4 weeks after COVID-19
    - 0.2mg/kg x 2 days: 88% of patients reported “total improvement”
    - Dose then increased to 0.4mg/kg x 2 days: 94% of patients reported “total improvement”
# In-Progress Controlled Trials Concluding Soon

<table>
<thead>
<tr>
<th>Country</th>
<th># Patients</th>
<th>Anticipated Pub Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bulgaria</td>
<td>n = 120</td>
<td>Any Day</td>
</tr>
<tr>
<td>Brazil</td>
<td>n = 170</td>
<td>Any Day</td>
</tr>
<tr>
<td>Columbia</td>
<td>n = 450</td>
<td>Any Day</td>
</tr>
<tr>
<td>Argentina</td>
<td>n = 500</td>
<td>February 5\textsuperscript{th}</td>
</tr>
<tr>
<td>Mexico</td>
<td>n = 3,000</td>
<td>February 5\textsuperscript{th}</td>
</tr>
</tbody>
</table>
Bulgaria Study – Newspaper Report 1-28-21

- Phase 2, multi-center, double blind, placebo-controlled RCT
  - N=100 patients over 12 hospitals
  - 0.4 mg/kg daily for 3 days after +PCR (within 7 days of symptoms)
    - Re-tested PCR on days 3 and 4
    - Quantitative assessment of clinical condition using WHO scale (9 category)
  - Reported statistically significant impacts on:
    - Improvement in rates of clinical clearance
    - Improvement in clinical condition
    - Improvement in inflammatory markers
Dr. Andrew Hill, University of Liverpool, UK
Consultant to the World Health Organization on Ivermectin for COVID-19

Recent Quotes Pertaining to Ivermectin

“The purpose of this report is to forewarn people that this is coming: get prepared, get supplies, get ready to approve it. We need to be ready.”  
- Dr. Andrew Hill

The probability that the measured impacts on survival of ivermectin is due to chance is “1 in 5,000”  
- Dr. Andrew Hill

“Millions of vaccine doses were manufactured/purchased ‘at risk’ by countries before efficacy was confirmed. Can we start to upscale ivermectin as well?”  
- Dr. Andrew Hill
THE REAL-WORLD EVIDENCE

- We must thank these sources for the clinical and epidemiologic data to follow:

  - **Juan Chamie**, a data analyst from Columbia, now living in the US, has been compiling and analyzing data from South American countries since April after first reports of effectiveness of ivermectin in Columbia and Peru.

  - **Alan Cannell**, a British engineer who lives in Brazil who also stated compiling data on case counts and deaths in the Brazilian cities that initiated ivermectin distribution campaigns.

  - **TrialSiteNews**, for meticulously and immediately posting news of all the emerging trials evidence reviewed, as well as the work of Chamie and Cannell above.

  - **Paul E. Marik, MD** – for getting the FLCCC to focus on ivermectin 😊
Figure 12. Total Deaths/Population and Case Incidence for COVID-19 / Population in population older than 60 years old for eight Peruvian states deploying mass ivermectin treatment.
Figure 13. Case Fatality Rate in population older than 60 years old for eight Peruvian states deploying mass ivermectin treatment.
“Mega Operacion Tayta” – August 2020
Prophylaxis protocol targeting elderly and most risk challenged people in Peru
In Lima, Peru (in red). No ivermectin distribution campaign took place.
A Tale of Three Cities in Brazil

- Case count decreases in Brazilian cities with ivermectin distribution programs
  (yellow rows are cities that distributed ivermectin, neighboring city in same region did not)

<table>
<thead>
<tr>
<th>Region</th>
<th>Confirmed new cases/month</th>
<th>June</th>
<th>July</th>
<th>August</th>
<th>Population 2020 (1,000)</th>
<th>% August vs. June/July</th>
</tr>
</thead>
<tbody>
<tr>
<td>South</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Itajaí</td>
<td>2,123</td>
<td>2,854</td>
<td>998</td>
<td>223</td>
<td>223</td>
<td>40%</td>
</tr>
<tr>
<td>Chapecó</td>
<td>1,760</td>
<td>1,754</td>
<td>1,405</td>
<td>224</td>
<td>80%</td>
<td></td>
</tr>
<tr>
<td>North</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macapá</td>
<td>7,966</td>
<td>2,481</td>
<td>2,370</td>
<td>503</td>
<td>45%</td>
<td></td>
</tr>
<tr>
<td>Ananindeua</td>
<td>1,520</td>
<td>1,521</td>
<td>1,014</td>
<td>535</td>
<td>67%</td>
<td></td>
</tr>
<tr>
<td>North East</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Natal</td>
<td>9,009</td>
<td>7,554</td>
<td>1,590</td>
<td>890</td>
<td>19%</td>
<td></td>
</tr>
<tr>
<td>João Pessoa</td>
<td>9,437</td>
<td>7,963</td>
<td>5,384</td>
<td>817</td>
<td>62%</td>
<td></td>
</tr>
</tbody>
</table>
# A Tale of Three Cities in Brazil

<table>
<thead>
<tr>
<th>REGION</th>
<th>STATE</th>
<th>CHANGE IN AVERAGE DEATHS (%) PREVIOUS WEEK COMPARED TO 2 WEEKS AGO (A)</th>
<th>TOTAL COVID RELATED DEATHS</th>
<th>DEATHS/100K</th>
</tr>
</thead>
<tbody>
<tr>
<td>South</td>
<td>Santa Catarina</td>
<td>-36 %</td>
<td>2529</td>
<td>35,6</td>
</tr>
<tr>
<td></td>
<td>Paraná</td>
<td>-3 %</td>
<td>3823</td>
<td>35,3</td>
</tr>
<tr>
<td></td>
<td>Rio Grande do Sul</td>
<td>-5 %</td>
<td>4055</td>
<td>33,4</td>
</tr>
<tr>
<td>North</td>
<td>Amapá</td>
<td>-75 %</td>
<td>678</td>
<td>80,2</td>
</tr>
<tr>
<td></td>
<td>Amazonas</td>
<td>-42 %</td>
<td>3892</td>
<td>93,9</td>
</tr>
<tr>
<td></td>
<td>Pará</td>
<td>13 %</td>
<td>6344</td>
<td>73,7</td>
</tr>
<tr>
<td>North</td>
<td>Rio Grande do</td>
<td>-65 %</td>
<td>2315</td>
<td>66</td>
</tr>
<tr>
<td>East</td>
<td>Norte</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ceará</td>
<td>62 %</td>
<td>8666</td>
<td>95,1</td>
</tr>
<tr>
<td></td>
<td>Paraíba</td>
<td>-30 %</td>
<td>2627</td>
<td>65,4</td>
</tr>
</tbody>
</table>
### States in India – Ranking by # cases/100,000

<table>
<thead>
<tr>
<th>State</th>
<th>Total Cases</th>
<th>Cases per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delhi</td>
<td>634,072</td>
<td>3,777</td>
</tr>
<tr>
<td>Goa</td>
<td>52,977</td>
<td>3,632</td>
</tr>
<tr>
<td>Ladakh</td>
<td>9,687</td>
<td>3,532</td>
</tr>
<tr>
<td>Puducherry</td>
<td>38,878</td>
<td>3,115</td>
</tr>
<tr>
<td>Kerala</td>
<td>893,639</td>
<td>2,675</td>
</tr>
<tr>
<td>Chandigarh</td>
<td>20,749</td>
<td>1,966</td>
</tr>
<tr>
<td>Andhra Pradesh</td>
<td>887,066</td>
<td>1,796</td>
</tr>
<tr>
<td>Maharashtra</td>
<td>2,010,948</td>
<td>1,790</td>
</tr>
<tr>
<td>Karnataka</td>
<td>936,426</td>
<td>1,533</td>
</tr>
<tr>
<td>Dadra and Nagar Haveli and Daman and Diu</td>
<td>3,394</td>
<td>1,395</td>
</tr>
</tbody>
</table>

- **Andaman and Nicobar Islands**: 1 case per 26 people
- **Uttar Pradesh Population**: 237 million
- **Bihar Population**: 124 million
- **1 case per 333 people**

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FRONT LINE COVID-19 CRITICAL CARE ALLIANCE • FLCCC.NET
PREVENTION & TREATMENT PROTOCOLS FOR COVID-19
AUGUST 8

AUGUST 22
In the capitol Lucknow, 40 kiosks opened to distribute Ivermectin.
Late July – Ivermectin adopted in early treatment. Followed by reports of ivermectin is being distributed as prophylaxis/prevention.
What Happened in New Delhi?

COVID-19 in India
Daily deaths in Delhi

Covid-19: Inspection teams flag violations by private hospitals

Change in COVID-19 treatment protocol: Ivermectin drug not to be used, ICMR issues advisory on Feluda paper strip test

News sources:
COVID-19 IN PARAGUAY
COVID-19 in MEXICO

Cases per 100,000 people before August 1st 2020
Cases per 100,000 people after August 1st 2020

Source: https://www.gob.mx/salud/documentos/datos-abiertos-151127
Analyst: Juan Chamie Juanjchamie@gmail.com

Chiapas is the only state distributing ivermectin to treat COVID-19. The distribution started on July 2020.

Updated 12/2/20
COVID-19 in MEXICO

Deaths per 100,000 people before August 1st 2020  Deaths per 100,000 people after August 1st 2020

Source: https://www.gob.mx/salud/documentos/datos-abiertos-15212?questions?
Analyst: Juan Chamie juanichamie@gmail.com

Chiapas is the only state distributing ivermectin to treat COVID-19
The distribution started on July 2020

Updated 12/2/20
Chiapas is the only state distributing Ivermectin
Deaths reduced

COVID-19 in MEXICO

COVID-19 in MEXICO
COVID-19 in MEXICO
July 1, 2020 - Jan 6, 2021

COVID-19 Deaths - Cumulative

Only State to treat with ivermectin

Update (Jan 10, 2021) - latest chart from Juan Chamie for Chiapas:

Source: [https://www.gob.mx/salud/documentos/datos-abiertos-152127?Questions]
Section IV

Select U.S. Hospitals Utilizing Ivermectin & Further N.I.H. Discussion
Select U.S. Hospitals Utilizing Ivermectin in Protocol

United Memorial Medical Center Hospital – Houston, Texas
- Dr. Joseph Varon (“The COVID Hunter”); one of the FLCCC Alliance founding physicians
- Been using our I-MASK+ and MATH+ protocols (with ivermectin) since last March
- His mortality statistics are included in a peer-reviewed and published paper through The Journal of Intensive Care Medicine
  - 5.1% mortality for hospitalized COVID-19 patients vs. national average of 22.9%

Broward Health System – Broward County, Florida
- Five-hospital system
- Been using our I-MASK+ and MATH+ protocols (with ivermectin) since last March
- Their mortality statistics are included in a peer-reviewed and published paper through CHEST medical journal
  - Under 10% mortality for hospitalized COVID-19 patients vs. national average of 22.9%

Brockton Hospital – Outside of Boston, Massachusetts
- 200 bed hospital; 16 ICU beds
- Began using ivermectin for ICU patients only in December 2020
- January 2021: ICU mortality rate already dropped from 46% to 25%
Select U.S. Hospitals & Other Providers Utilizing Ivermectin

Dayton Ohio VA Hospital
Univ. Tennessee Hospital
Lincoln Hospital & N. Basin Medical Clinics, WA

No Picture
No Picture
No Picture

Urgent Care Chain
Florida Keys
Assisted Living Company
Southern U.S.
10 Multi-State Tele-Health Operators

Worldwide:
Uttar Pradesh, Chiapas, MX; Belize; Macedonia; El Salvador; Bolivia; Venezuela; Panama; Peru
Countries and States that have adopted Ivermectin into Treatment Guideline

- Peru
- Bolivia
- South Africa
- Zimbabwe
- Slovakia
- Macedonia
- State of Uttar Pradesh (Pop. 231 million)
- State of Bihar (Pop. 124 million)

Regions marked with green indicate where Ivermectin is approved, orange indicates temporary adoption, and green indicates approval for treatment guidelines.
Ivermectin: A “Bridge to” and “Safety-Net for” an Effective Vaccine Campaign Globally

- Long lead-time to broad distribution (U.S. and globally)

- Issues with early adoption
  - Most assisted living & skilled nursing companies in U.S. (only 30% - 40% of community employees currently willing to take the vaccine – including employed registered nurses)
  - Recent survey of registered nurses in the U.S. also indicated lower that anticipated willingness at this time

- What category of people ARE NOT helped by a vaccine? Those who already have COVID-19, and those who will contract it in the future.

- Vaccines are not 100% effective in protecting against infection

- All viruses mutate (Brazil mutation E384 strain – resistant to neutralizing antibodies)

- Don’t yet know how long the vaccines will protect from infection (too early; we don’t have any data)
Why isn’t everyone using it? Let’s review some criticisms:

- “Majority of the trials were not randomized controlled trials” – FALSE
  - 20 of the 32 controlled trials are... randomized.. and include over 2,800 patients

- “Majority of the studies were small” – FALSE
  - Ten of the 17 RCT’s included more than 100 patients each
  - * The highest form of medical evidence in support of a therapy is a “meta-analysis of randomized, controlled trials” – not any one individual, even large, trial

- “Majority of studies are observational, uncontrolled trials” – FALSE
  - All the observational trials have control groups, well matched or propensity matched
  - OCT’s and RCT’s have reached similar conclusions throughout the history of evidence-based medicine
  - OCT’s are the most ethical approach to studying effective therapies in a pandemic

- “Majority of studies have not been published in peer-reviewed journals” – IRRELEVANT
  - 12 of the 32 trials have been published in peer-reviewed journals
  - Every therapeutic in COVID-19 was adopted from pre-print data prior to peer review
    - Remdesivir, corticosteroids, monoclonal antibodies, convalescent plasma come to mind
    - *** Inoculations of vaccines began.. prior to the availability of a pre-print version of the vaccine trial
    - ** Hydroxychloroquine and convalescent plasma were widely adopted before any data supported use

- “Majority of the trials were performed abroad and are not generalizable to our patients” – ABSURD
  - This deserves no further comment except to note it’s undercurrent of racism, ethnocentrism, and/or immovable skepticism
“All truth passes through three stages:”

FIRST
“It is ridiculed”

SECOND
“It is violently opposed”

THIRD
“It is accepted as self-evident”

-Arthur Schopenhauer
19th Century German Philosopher
NIH Recommendation Rating Scheme

<table>
<thead>
<tr>
<th>Strength of Recommendation</th>
<th>Quality of Evidence for Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: Strong recommendation for the statement</td>
<td>I: One or more randomized trials with clinical outcomes and/or validated laboratory endpoints</td>
</tr>
<tr>
<td>B: Moderate recommendation for the statement</td>
<td>II: One or more well-designed, nonrandomized trials or observational cohort studies</td>
</tr>
<tr>
<td>C: Optional recommendation for the statement</td>
<td>III: Expert opinion</td>
</tr>
</tbody>
</table>

- On August 27\textsuperscript{th}, the NIH recommended “against the use of ivermectin outside of clinical trials” with an A-III Rating
  - A = STRONG
  - III = EXPERT OPINION ONLY

- On January 6\textsuperscript{th}, the FLCCC Alliance presented the data on ivermectin to the 22 member NIH Panel
- On January 14\textsuperscript{th}, the NIH upgraded their recommendation:
NIH Guideline Committee Recommendation on Ivermectin use in COVID-19

January 14, 2021

- “The COVID-19 Treatment Guidelines Panel has determined that currently there are insufficient data to recommend either for or against the use of ivermectin for the treatment of COVID-19. Results from adequately powered, well-designed, and well-conducted clinical trials are needed to provide more specific, evidence-based guidance on the role of ivermectin for the treatment of COVID-19.”

- Same recommendation as for monoclonal antibodies and convalescent plasma
- FLCCC Alliance’s Open Rebuttal Letter to the N.I.H.: [https://tinyurl.com/yxu87m5s](https://tinyurl.com/yxu87m5s)
Guideline Recommendations - Cochrane Method

- **Certainty of evidence** – Desirable vs. undesirable effects - *some uncertainty*
- **Values and Preferences** – mortality, avoid hospitalization - *no uncertainty*
- **Resources** of ivermectin vs. hospital/ICU resources - *no uncertainty*
- **Costs** of ivermectin vs. hospital/ICU – *no uncertainty*
- **Equity** – equitably offered – poor/rural/home/needle fear - *no uncertainty*
- **Acceptable** to key stakeholders – *no uncertainty*
- **Feasible/Safe** – can supply meet demand? – *some uncertainty in short term*
NIH Guideline Recommendation on Prophylaxis/Preventative for COVID-19

Prevention and Prophylaxis of SARS-CoV-2 Infection

Last Updated: December 17, 2020

Summary Recommendations

• The COVID-19 Treatment Guidelines Panel (the Panel) recommends against the use of any agents for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pre-exposure prophylaxis (PrEP), except in a clinical trial (AIII).
• The Panel recommends against the use of any agents for SARS-CoV-2 post-exposure prophylaxis (PEP), except in a clinical trial (AIII).

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies; III = Expert opinion
Section V

Conclusions & Call to Action
CONCLUSION

• Ivermectin, given its potent efficacy in both prevention and treatment in all phases of the disease should be considered:
  
  • The standard of care in all phases of disease
  
  • Both a “bridge to” and “safety net for” vaccination efforts
  
• The consistency and magnitude of benefit amongst numerous trials of varying designs from multiple centers and countries around the world is unique in both the history of evidence-based medicine and my career
  
  • The reproducible, large magnitude impacts on multiple clinical outcomes is the most profound of any intervention in any disease model that I have studied
  
  • I personally believe its efficacy in COVID-19 rivals that of the discovery of penicillin in treating bacterial infections

  • One difference: Penicillin required no RCT’s before use, yet in 2021, ivermectin the former requires dozens of RCT’s and thousands of patients subjects before use.
YPO & Other “Co-Champions” Needed

FLCCC Mission:
- Advocate widely until ivermectin becomes the standard of care globally in the prevention and COVID-19

Please Consider Supporting Our Work & Our Mission in any Way You Can:
- Family, business, and broad centers-of-influence
- Broader exposure throughout YPO globally (i.e., top leadership, international networks, etc.)
- Contacts in the press/media
- Pressure on national health agencies globally via relationships
Visit Our Website:  www.flccc.net

FAQs & Tele-Health Resources for prescriptions

I-MASK+:  Prophylaxis & Early Outpatient Treatment protocol

MATH+: Hospital Treatment Protocol

Note:  We have no commercial interests; no conflicts of interest

To Receive this Slide Deck and/or the Video Recording of this Event to Pass Along, please email:

jhanson@ahinvestors.com
Protect Yourselves and Others by Acting on this Information

- Start by sending this video presentation & slide deck to your family, friends, employees, colleagues and professional networks

- Include links to the I-MASK+ & MATH+ protocols (found on our website)

- Obtain prescriptions for ivermectin from your doctor for appropriate members of your household; demonstrate to your physician the ability of ivermectin to prevent and treat every phase of COVID-19 illness by sharing the following:
  - Dr. Pierre Kory’s video presentation & slide deck https://covid19criticalcare.com/media/flccc-lecture-for-ypo-gold-on-ivermectin/
  - The FLCCC’s peer-reviewed SCIENTIFIC MANUSCRIPT; being published in a major U.S. journal “Frontiers in Pharmacology”
  - THE META-ANALYSIS of Dr. Andrew Hill, University of Liverpool, U.K. and Consultant to the W.H.O. on Ivermectin for COVID-19
  - THE FLCCC’s “GUIDE TO THE MANAGEMENT OF COVID-19”
  - The I-MASK+ PROPHYLAXIS & EARLY OUTPATIENT TREATMENT PROTOCOL

- If your physician still will not write a prescription out of willful ignorance, see this list of tele-health physicians that will https://www.exstnc.com/
Q & A
Ivermectin has anti-viral activity *in vitro* against a range of viruses.
Proposed Anti-Viral Mechanisms/SARS-CoV-2

- Binds to spike protein, disrupting binding with ACE-2 receptor – preventing entry
- Binds to multiple essential structural and non-structural proteins required for replication
- Binds to SARS-CoV-2 RNA dependent RNA polymerase, inhibiting viral replication
- Prevents importing mediated entry into cell nucleus?
The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro

Leon Caly\textsuperscript{a}, Julian D. Druce\textsuperscript{b}, Mike G. Catton\textsuperscript{b}, David A. Jans\textsuperscript{b}, Kylie M. Wagstaff\textsuperscript{b, c}

With a single addition of IVERMECTIN to Vero-hSLAM cells 2 h post infection with SARS-CoV-2 able to effect ~5000-fold reduction in viral RNA at 48 h.
Ivermectin inhibits SARS-CoV-2 in vitro

Relevance of IC$_{50}$ determined in vitro to clinical use?

- In vitro assay very different from clinical situation
  - Vero/hSLAM cells- monkey kidney- do not produce IFN
  - Lack immune responses
- Ivermectin accumulates in lungs and other tissues (3x-10x serum levels)
- Human lung cells- better IC$_{50}$
- Short exposure vs extended exposure
- Single dose vs repeat dosing
- Taken with food (3x level)

Red: peer-reviewed, published modelling of IVM lung concentration after 200ug/kg dose

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Pharmacology

- Binds selectively to glutamate-gated chloride ion channels in invertebrate nerve and muscle cells
- At therapeutic concentrations, the affinity of the drug to animal and human receptors are about 100 times less compared to the targeted helminth
- The Blood-Brain-Barrier prevents the entry of the drug in the central nervous system
- Ivermectin is highly lipophilic, rapidly absorbed (Tmax = 4 hours), strongly binds to plasma proteins, plasma T½ 16-28 hours
- Prolonged sequestration of the drug in lung tissues at 3 times the plasma concentration
- Hepatically metabolized by cytochrome P450 3A4, less than 1% excreted in the urine
Pharmacology

- 200ug/kg  Tmax ~ 60 ug/ml (fasted)
- 200ug/kg  Tmax about 150 ug/ml (with meal)
- 200ug/kg  Lung concentration 180 ug/g tissue (fasted)
- 200ug/kg  Lung concentration 450 ug/g tissue (with meal)

- IC$_{50}$ for alveolar cells 0.41 uM (105 ug/g)
  (uM to ng/ml conversion: 1uM = 750 ng/ml)
## Effects of Ivermectin on viral clearance in randomized trials – dosing on Day 1 only

<table>
<thead>
<tr>
<th>Study</th>
<th>Country (n)</th>
<th>Daily dose</th>
<th>Duration</th>
<th>Viral load endpoint</th>
<th>Result IVA vs Control</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mahmud et al</td>
<td>Bangladesh, n=363</td>
<td>12 mg</td>
<td>1 day (DB)</td>
<td>Detectable Day 14</td>
<td>8% vs 20%</td>
<td>p &lt; 0.001</td>
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<tr>
<td>Asghar et al</td>
<td>Pakistan, n=103</td>
<td>0.2 mg/kg</td>
<td>1 day</td>
<td>Undetectable Day 7</td>
<td>90% vs 44%</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Chowdhury</td>
<td>Bangladesh, n=112</td>
<td>0.2 mg/kg</td>
<td>1 day (DB)</td>
<td>Time to PCR neg</td>
<td>9 vs 9.3 days</td>
<td>p = n.s.</td>
</tr>
<tr>
<td>Podder et al</td>
<td>Bangladesh, n=62</td>
<td>0.2 mg/kg</td>
<td>1 day (OL)</td>
<td>Day 10 PCR neg</td>
<td>90% vs 95%</td>
<td>p = n.s.</td>
</tr>
<tr>
<td>Raad et al</td>
<td>Lebanon, n=100</td>
<td>0.2 mg/kg</td>
<td>1 day</td>
<td>Day 3</td>
<td>Ct values</td>
<td>p = 0.01</td>
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<tr>
<td>Mohan et al</td>
<td>India, n=157</td>
<td>0.2 – 0.4 mg/kg Elixir</td>
<td>1 day</td>
<td>Undetectable Day 5</td>
<td>48% vs 31%</td>
<td>p = n.s.</td>
</tr>
</tbody>
</table>
Could it work in Hospitalized Patients and why?

- IVERMECTIN appears to have profound anti-inflammatory activity
- A growing list of studies are identifying anti-inflammatory mechanisms
  - Inhibition of cytokine production after lipopolysaccharide exposure
  - Downregulation of transcription of NF-kB (most potent trigger of inflammation)
  - Limit the production of both nitric oxide and prostaglandin E₂
Avermectin exerts anti-inflammatory effect by downregulating the nuclear transcription factor kappa-B and mitogen-activated protein kinase activation pathway.

Signal transduction studies showed that avermectin significantly inhibits NF-κB p65 translocation into the nucleus.

Ivermectin inhibits LPS-induced production of inflammatory cytokines and improves LPS-induced survival in mice