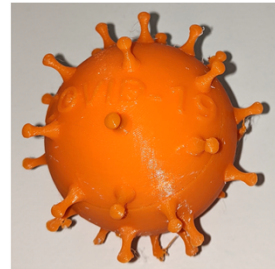


# The Coronavirus Pandemic: What are the Options?

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## About Nanotech Plus, LLC

- Alliance of Consultants established in 2004
- We provide the team matched to the project.  
[www.nanotechplus.net](http://www.nanotechplus.net), [www.nano-biz.com](http://www.nano-biz.com),  
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- We specialize in solving the challenges of commercializing advanced materials
- Focus areas: Pharmaceuticals, Energy Generation and Storage, Coatings, Composites, and more
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# Outline of the Talk

- 1) Setting the Stage: How bad is the current pandemic?
- 2) About the Disease:  
Contagion, Types, Time Course, Treatments
- 3) Description of the Coronavirus
- 4) What can be done to change the pandemic's course?
- 5) Diagnostic Needs and Development
- 6) Vaccine Challenges
- 7) Antiviral Development
- 8) Q+A

# Setting the Stage: How Bad is it?

## **Some Current Viral Epidemics**

- Examples: Coronaviruses (SARS, MERS), Zika, AIDS, Dengue, Polio, Influenza, Mononucleosis, Herpes, Norovirus, Hepatitis, Ebola, Measles, etc.

## **Some Current Bacterial Epidemics**

- Examples: E. Coli, Brucella (unpasteurized dairy), Listeria, Legionella, Gonorrhea, etc.

A recent listeria outbreak linked to mushrooms put 30 people in the hospital, 4 fatalities. See: <https://www.cdc.gov/listeria/outbreaks/enoki-mushrooms-03-20/index.html>

Brucella: [https://www.cdc.gov/brucellosis/exposure/unpasteurized-dairy-products.html?CDC\\_AA\\_refVal=https%3A%2F%2Fwww.cdc.gov%2Fbrucellosis%2Fexposure%2Fdrug-resistant-brucellosis-linked-raw-milk.html](https://www.cdc.gov/brucellosis/exposure/unpasteurized-dairy-products.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fbrucellosis%2Fexposure%2Fdrug-resistant-brucellosis-linked-raw-milk.html)

Legionella-form of pneumonia:<https://www.cdc.gov/legionella/>

## How Contagious is COVID-19?

<b>Virus</b>	<b>R0 (number of additional people infected from 1 infected individual )</b>
• COVID-19	2.0-3.3
• SARS	3.0
• MERS	2-5
• Ebola	2
• Measles	12-18
• Influenza	1.7-1.8 in 2009 H1N1 in US
• Zika	1.8-5.8

SARS, COVID-19: [https://www.ijidonline.com/article/S1201-9712\(20\)30123-5/fulltext](https://www.ijidonline.com/article/S1201-9712(20)30123-5/fulltext)

MERS: <https://www.ncbi.nlm.nih.gov/pubmed/28958834>

Zika: <https://www.ncbi.nlm.nih.gov/pubmed/26923081>

Utility of R0: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3935673/>

## Types of COVI-19 Infections

- Asymptomatic
- Mild Upper Respiratory Infection – similar to a cold
- Common – some lung involvement
- Severe – respiratory distress
- Multi-organ involvement – ICU  
Can involve heart, kidney, and even lead to gangrene  
60-70% of cases in the ICU die (Wuhan)
- Asymptomatic – common  
make up ~80% of cases

<https://www.biocentury.com/coronavirus/webinar/lessons-from-wuhan>

## Course of Infection

- From the mild to common cases:
  - 1) Viremia: 0 -10 days
  - 2) Acute: pneumonia 7-10 days to 14 days
    - viral production peaks
  - 3) Recovery: 14-21 days
- This is a longer course than SARS/MERS
- For severe cases – at 1-2 weeks
  - Need to get virus production under control

## Treatments: Current Anti Viral Usage

- In China, the following antivirals have been tried:
  - 1) Lopinavir/Ritonavir – no clear benefit in severe cases
  - 2) Remdesivir – no information as of 3/27/2020
  - 3) Interferon – not shown to be effective
  - 4) Chloroquine/hydroxychloroquine-positive results are unproven
  - 5) Azithromycin
- Only used in early stages of disease.
- In NYC – often using chloroquine/hydroxychloroquine/azithromycin – few side effects, but not very effective



## Mechanisms of Mortality

- Coinfection ~ → pneumonia ~ ½ the fatal cases
- Viral damage to lungs or other organs- especially heart!
  - 1) 20% of patients had myocardial damage – up to 50% mortality
  - 2) Patients with underlying cardiovascular conditions have higher mortality, but even previously healthy individuals have ~20% mortality
- Overly aggressive immune response ~ 20%  
Can be failure to control viremia or cytokine storm, i.e. low levels of virus present
- Myocardial damage can be direct viral infection or immune response

Sources: <https://jamanetwork.com/journals/jamacardiology/fullarticle/2763844>  
[https://wwwnc.cdc.gov/eid/article/26/6/20-0299\\_article](https://wwwnc.cdc.gov/eid/article/26/6/20-0299_article)

## Treatments: Anti Inflammatories

- If the person survives the coronavirus- then immune responses are similar to influenza infections
- Even If coronavirus viral production continues declines after 1-2 weeks, immune system responses can be fatal – not directly from virus!
- Therapies for severe cases:
  - 1) Steroids- highly debated!
  - 2) Very high doses (2 grams) iG – can be used in earlier stages
  - 3) Anti- IL-6 Tocilizumab- efficacy hard to evaluate.
  - 4) Other immune suppressors

Other treatments: anti coagulants- up to 2 weeks. New pulmonary anti-inflammatory: Immunomet 156 being evaluated.

- Summary: some immune suppression and anti coagulants can be life saving!

## About Coronaviruses

- Coronaviruses are the largest RNA viruses at 125 nm  
7 infect humans
- SARS Co V2 – 30kb. 20 kb – non-structural, 10 kb structural and accessory proteins. 80% homology with SARS-CoV1, 96% with some bat coronaviruses
- Enveloped and has 4 proteins: S (spike), E (envelope), M (membrane), N (nucleocapsid)
- Structural proteins not conserved!

Sources: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4369385/>

## Mechanism of SARS CoV2

- SARS CoV1 and SARS CoV2 use the ACE2 pathway to gain entry into the cell
- Angiotensin – Converting-Enzyme 2 (ACE2) primarily is involved in maturing angiotensin- important in controlling blood pressure and other functions
- ACE2 is expressed in heart, lungs, kidney and intestines
- CoV2 uses the spike protein (S) to gain entry
- S1 binds to the ACE2 site, S2 does membrane fusion
- Note that MERS uses a different mechanism to enter cells

Science: 27, Mar. 2020, p. 1444.

# How do we change the course of the Pandemic?

## **Passive Measures**

- 1) Track cases/contacts.
- 2) Diagnostics:
  - A) Direct virus detection  
Large testing labs gearing up
  - B) Detection of antibodies  
POC tests could be available  
in less than 2 months
- 3) Isolation/Social Distancing
- 4) Protective Equipment

## **Active Measures**

- 1) Better Models!
- 2) Vaccines
- 3) Antivirals

## Diagnostic Needs: Detection

- Detection Methods:
  - Direct viral detection (PCR)
  - Indirect detection: Antibodies
- Direct detection allows determination of infected individuals and viral loads  
Highly accurate – but time consuming
- Indirect detection shows who is currently infected or has survived and is now immune  
Less accurate, faster, can be POC- BD/Biomedomics
- In competition with WHO, CDC developed direct detection kits – but were not accurate

<https://www.nature.com/articles/d41587-020-00010-2>

<https://wyss.harvard.edu/news/news-the-wyss-institutes-response-to-covid-19-beating-back-the-coronavirus/>

<https://www.washingtonpost.com/investigations/2020/04/03/coronavirus-cdc-test-kits-public-health-labs/?arc404=true>

## Better Models Needed!

### **In Vivo**

- Challenges: virus replicates in numerous animal models, but fails to cause disease even in non-human primates
- Can cause sneezing in ferrets
- Humanized mouse model developed for SARS/MERS Scaleup underway- Jackson Labs in several weeks

### **In Vitro**

- Wyss Institute Lab on a Chip – being commercialized by Emulate, Inc
- Lung model has been used in influenza – but not ready for COVID-19

<https://www.jax.org/news-and-insights/2020/february/introducing-mouse-model-for-corona-virus>

<https://wyss.harvard.edu/news/news-the-wyss-institutes-response-to-covid-19-beating-back-the-coronavirus/>

# Vaccine Development

## **Good News: Lots of Companies**

### **Trying New Technology**

(Selected companies)

- Adenovirus: Altimune, J+J, Vaxart
- Nucleotide: Arcturus, BioNTech, Curevac, Inovio, LinearRX, Moderna, Zydus Cadila
- Protein: Generix, Heat Biologics, Vaxil Biotherapeutics
- Recombinant/Attenuated: Clover/GSK, Codagenix, Novavax, Sanofi, Tonix, Vaxart
- VLP: Geovax, iBio, Medicago, Novavax

## **Bad News**

- Vaccine development is typically 5 years or more
- Vaccines can be harmful!
  - a) Antibody Dependent Enhancement (ADE) and
  - b) Th2 immunopathology
- Only Sanofi of the “Big 4” vaccine manufacturers has mounted a COVID-19 specific effort- others choosing to partner instead

Sources: <https://www.pnas.org/content/early/2020/03/27/2005456117>

<https://www.wired.com/story/everything-you-need-to-know-about-coronavirus-vaccines/>

<https://www.genengnews.com/a-lists/how-to-conquer-coronavirus-top-35-treatments-in-development/>

Most detailed: <https://www.nature.com/articles/d41587-020-00005-z>

The vaccine for Ebola story: <https://www.statnews.com/2020/01/07/inside-story-scientists-produced-world-first-ebola-vaccine/>



# Antiviral Development

## RNAi

- Vir Biotechnologies:  
very well funded  
Partnered with Alnylam  
GSK recently funded  
with \$250M  
Challenges: few  
successful RNAi  
drugs in market –  
delivery systems are  
challenging
- Sirnaomics

## Viral Blockers

- Apeiron: protein-based  
technology  
– In clinical trials in  
China
- Nanoviricides: ligands  
mimicking binding site  
bound to a soft polymer  
– Developed MERS  
ligands prior

<https://www.nature.com/articles/d41587-020-00005-z>

## Antiviral Development, Cont'd

### **mAb**

- Abcellera – partnered with Lilly  
Developed 500 mAb from one patient
- Beijing Defengrei – in clinical trials  
Targeting Factor 5A
- InflaRx – targeting Factor 5A
- Harbor Biomed – partnered with Mt. Sinai  
Targeting Spike protein
- ImmunoPrecise Antibodies –  
partnered with EVQLV, Ligand  
Pharmaceuticals

### **Other**

- Pharmamar –  
natural product  
from tunicates  
targeting  
elongation factor  
1-A

Q+A



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