Transmissibility of emerging pathogens: Estimation, risk assessment, and control

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**Epidemic or pandemic emergence:** a new pathogen entering the human population and establishing *sustained transmission.*

i.e. reproductive number, \( R > 1 \)

→ human-to-human transmissibility is the heart of pandemic risk.

Both *efficiency* (especially sub-/supercritical) and *routes of transmission.*
<table>
<thead>
<tr>
<th>Circulation in reservoir</th>
<th>Cross-species spillover</th>
<th>Subcritical transmission ($R &lt; 1$)</th>
<th>Epidemic or pandemic spread ($R &gt; 1$)</th>
</tr>
</thead>
</table>

Characterizing and quantifying transmission is essential for **risk assessment** of possible pandemic threats and for **prevention and control** once a pandemic has begun.
Building blocks of transmissibility

Human-to-human transmissibility
• Inherent biology of host-pathogen interaction

**Effective** $R = R_0 \times \text{susceptibility}$

Susceptibility of the novel host population
• Population immunity against ‘novel’ viruses
Outline

Characterizing transmissibility in the field
- Superspreading
- Subcritical zoonoses at the animal-human interface

Unpacking transmissibility in the lab
- Transmission experiments
- Virological experiments
  - Viral stability in the environment
  - Connection to transmission risk
  - Effects of temperature and humidity

Susceptibility of the novel host population
- Case studies: monkeypox and influenza
- COVID-19 and beyond
Superspreading and the effect of individual variation on disease emergence

J. O. Lloyd-Smith\textsuperscript{1,2}, S. J. Schreiber\textsuperscript{3}, P. E. Kopp\textsuperscript{4} & W. M. Getz\textsuperscript{1}

Analyzed contact tracing data...

... to show that superspreading (i.e. substantial individual variation in infectiousness) is ubiquitous in infectious diseases.

\textit{Lloyd-Smith et al, Nature (2005)}
Superspreading and the effect of individual variation on disease emergence

J. O. Lloyd-Smith\textsuperscript{1,2}, S. J. Schreiber\textsuperscript{3}, P. E. Kopp\textsuperscript{4} & W. M. Getz\textsuperscript{1}

Analyzed contact tracing data...

... to show that superspreading (i.e. substantial individual variation in infectiousness) is ubiquitous in infectious diseases.

Introduced a stochastic modeling framework to analyze consequences:

Greater individual variation

\(\rightarrow\) Introductions more likely to die out.

\(\rightarrow\) Major outbreaks are explosive.

\(\rightarrow\) Minor outbreaks are highly variable.

\textit{Lloyd-Smith et al, Nature (2005)}

Estimating subcritical transmissibility from field data

For subcritical zoonoses (i.e. those with $0 < R < 1$), a key challenge is to disentangle contributions of zoonotic spillover versus human-to-human transmission.

All models of directly-transmitted zoonoses (as of 2009)

- **Epidemics ($R > 1$)**
- **Subcritical ($0 < R < 1$)**
- **Spillover**
- **Reservoir**

Big gap right where the zoonotic action is.

*Lloyd-Smith et al, Science (2009)*
Estimating subcritical transmissibility from field data

Three new methods using attainable data (case onset dates or cluster sizes) and addressing common challenges (imperfect case detection, missing location data, unknown denominator of sites at risk).

Blumberg & Lloyd-Smith, Epidemics (2013)
Estimating subcritical transmissibility from field data

Three new methods using attainable data (case onset dates or cluster sizes) and addressing common challenges (imperfect case detection, missing location data, unknown denominator of sites at risk).

Monique Ambrose

Monkeypox in the Congo basin, 1980-86

Assumed scale of mixing

Reproductive number, $R$

Spillover rate

Rational control for subcritical zoonoses

Model-based guidance for how to prioritize control measures to reduce spillover versus human-to-human transmission.

Mummah et al, One Health Outlook (2020)
Rational control for subcritical zoonoses

Model-based guidance for how to prioritize control measures to reduce spillover versus human-to-human transmission.

Reducing spillover $\rightarrow$ linear effect on total incidence

Reducing $R$ $\rightarrow$ nonlinear effect, greater as $R \rightarrow 1$

Reducing both $\rightarrow$ always best.

Reactive control: reduce spillover then switch to reducing $R$ after outbreak discovered $\rightarrow$ almost as good.

*Mummah et al, One Health Outlook (2020)*
Rational control for subcritical zoonoses

Model-based guidance for how to prioritize control measures to reduce spillover versus human-to-human transmission.

Optimal strategy depends on resources available, and on relative cost. With unlimited resources, always better to stop all spillover.

Mummah et al, One Health Outlook (2020)
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Susceptibility of the novel host population
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Assessing transmissibility without data from humans

When new viruses are discovered, e.g. by genetic surveillance or gain-of-function experiments, can we estimate their ability to infect humans or transmit among humans from indirect evidence?
Assessing transmissibility without data from humans

Goal: Test whether ferret studies give useful information about human-to-human transmission.
Meta-analysis of ferret transmission studies

Gathered data:

- all ferret transmission experiments using influenza strains isolated from humans. 10 subtypes represented, 4 seasonal and 6 zoonotic.

Meta-analysis of ferret transmission studies

Statistically speaking:

if more than 2/3 of ferrets infected, the strain is likely to be supercritical.

Meta-analysis of ferret transmission studies

Conclusion
Ferret experiments are a valid approach for screening influenza strains for pandemic potential, but corroborating evidence is needed.

Caveats and challenges
• Out-of-sample prediction is inherently risky.
• Small sample sizes → huge binomial uncertainties. Wasting information.
• Crude prediction (sub- vs supercritical)

_Buhnerkempe, Gostic et al, eLife (2015)_
Use within-host viral titer data to get higher-resolution picture of transmission.

Assume exponential growth in early phase of infection

→ Can estimate when infection occurred, not just whether it occurred.

Park et al, dissertation (2017)
Illustration: an experiment with 6 transmission pairs

Conventional output
4/6 contact ferrets infected

Can estimate continuous hazard rate of infection
(aka ‘force of infection’)
Cross-scale model for ferret experiments

Use MCMC to jointly estimate within-host growth rate and force of infection, while imputing time of infection for each ferret pair.

Test case: analyzed all CDC data on transmission experiments, by subtype.

→ Better resolution than proportion infected.

→ Joint estimate of within- and between-host fitness.

*Park et al, dissertation (2017)*
Estimating risk from uncharacterized viruses

Use models of intracellular life cycle within-host dynamics to link insights from virologic assays

- Can within-host fitness be predicted from *in vitro* data?
- Can transmission by predicted from within-host fitness, tissue tropism, and other traits measurable in the lab?

*Image credit: Held et al, PLOS Comp Biol (2013)*
How long can SARS-CoV-2 remain infectious in the environment?

→ Determines infection risk from fomite and airborne exposure

• Virologist collaborators at NIH Rocky Mountain Labs put live virus on various surfaces, and sprayed into a mist, and measured how long they could still detect live virus afterward.

• We modeled the data to extract the robust findings, given limited data.
  • Exponential decay model fitted by Bayesian regression
COVID-19 – From virologic traits to transmission risk

Van Doremalen et al. 2020, NEJM
COVID-19 – From virologic traits to transmission risk

• Statistical modeling of the data to estimate the decay rate...
  ... which enabled us to estimate the half-life in each environment

Van Doremalen et al. 2020, NEJM
COVID-19 – From virologic traits to transmission risk

**Raw data**

**Decay rate**

**Half-life**
WHO considers ‘airborne precautions’ for medical staff after study shows coronavirus can survive in air.

The COVID-19 Coronavirus May Travel in Aerosols
Several studies have indicated that SARS-CoV-2 might be spread through air, but not all experts are convinced.

Los Angeles Times
A choir decided to go ahead with rehearsal. Now dozens of members have COVID-19 and two are dead.

Yes you should clean surfaces, but COVID often spreads via aerosols – hence ‘distancing’.
COVID-19 – From virologic traits to transmission risk

Modeling virological data to estimate transmission risk

Case study: aerosol infection

• For an airborne infection event, you need three processes to occur

- Creation of aerosolized virus
- Virus remains viable and present in the air
- Susceptible human is exposed and infected

Unpublished work led by graduate student, Dylan Morris.

Please do not ‘borrow’ without credit!

Dylan Morris
Amandine Gamble

Morris et al., unpublished
COVID-19 – From virologic traits to transmission risk

Modeling virological data to estimate transmission risk

Case study: aerosol infection

• For an airborne infection event, you need three processes to occur

    Creation of aerosolized virus

    +

    Virus remains viable and present in the air

    +

    Susceptible human is exposed and infected

• Built mathematical model to integrate known factors

  Virus decay rate, aerosol physics, particle size distributions, dose-response theory

• Renormalized to ID_{50} units to compartmentalize the unknowns

  Aerosolization rates, infectious dose

  Morris et al., unpublished
Consider scenarios of contamination and exposure, which together give rise to an exposure dose and consequent risk of infection.

Hypothetical examples:

**Contamination**
- Infected person **coughs** in a room for 10 minutes

**Exposure**
- Susceptible person spends **1 minute** in room, without PPE
- Susceptible person spends **5 minutes** in room, without PPE

**Dose**
- 1 ID$_{50}$
- 5 ID$_{50}$

*Morris et al., unpublished*
Consider scenarios of contamination and exposure, which together give rise to an exposure dose and consequent risk of infection.

Hypothetical examples:

**Contamination**

- **Intubation** of patient at peak viral load

**Exposure**

- Susceptible person spends 1 minute in room, **without PPE**
  - Dose: $10 \text{ ID}_{50}$

- Susceptible person spends 1 minute in room, **wearing N95 respirator**
  - Dose: $0.1 \text{ ID}_{50}$

*Morris et al., unpublished*
COVID-19 – From virologic traits to transmission risk

- Modeled three exposure scenarios: low-risk, medium-risk, high-risk events

  - **Ventilation** rapidly dominates effects of inactivation and particle settling
  - Initial **contamination load** has sustained influence on viable viral load.
COVID-19 – From virologic traits to transmission risk

- Modeled three exposure scenarios: low-risk, medium-risk, high-risk events

Ventilation is the most important factor in reducing airborne risk

- No ventilation → risk lasts for hours
- High-ventilation hospital settings → risk lasts 10s of minutes

Morris et al., unpublished
COVID-19 – From virologic traits to transmission risk

• Modeled three exposure scenarios: low-risk, medium-risk, high-risk events

Compute waiting time needed to reduce risk to specified levels

e.g. medium-risk event (contamination of 10 ID50s)

   in Operating Room (12 ACH), need to wait 30 minutes for infection risk to drop to 1 in 1000.
   in Patient Room (4 ACH) need to wait 2 hours
   in unventilated space (0 ACH), 16 hours.

Morris et al., unpublished
Environmental effects on SARS-CoV-2 stability

- Virus stability is known to be affected by temperature and humidity
  - Factor contributing to seasonality of respiratory viruses (alongside host factors and contact patterns)
  - Will govern infection risk in particular environments, indoors and outdoors.
- But effects of temperature and humidity are not well understood, for SARS-CoV-2 or in general.

- **Experiments**: measure stability of SARS-CoV-2 deposited on plastic surfaces across different temperatures and humidities.
  
  - 10 °C × 40%
  - 22 °C × 65% relative humidity
  - 27 °C × 85%

- **Modeling**: to extract maximum insight from sparse data, and seek generalizability.
Environmental effects on SARS-CoV-2 stability

- Half-lives vary **20-fold** across measured conditions
- (even more when transient phase with excess water included)
- Higher temperature causes faster inactivation.
- Effect of humidity is **non-monotonic**, with consistent U-shape

*Morris*, *Yinda*, *Gamble* et al., unpublished
Mechanistic model for temperature and humidity effects

**Premise:**
Inactivation is driven by chemical reactions (with unknown reactants)

**Temperature dependence** governed by Arrhenius equation

\[ k = A \exp \left( -\frac{E^a}{RT} \right) \]

- \( k \) is reaction rate
- \( E^a \) is activation energy
- \( A \) is asymptotic reaction rate at high \( T \)

*Morris*, Yinda*, Gamble* et al., unpublished
Mechanistic model for temperature and humidity effects

**Premise:**
Inactivation is driven by chemical reactions (with unknown reactants)

**Humidity dependence** has two distinct regimes, divided by the **efflorescence relative humidity** (ERH)

*Yang et al, PLOS ONE (2012)*

**Below the ERH:** electrolytes effloresce out of solution to form a crystal.

**Above the ERH:** evaporation reaches equilibrium with reactants in solution, with concentration $\propto 1/$humidity.

*Morris*, *Yinda*, *Gamble* et al., unpublished
Mechanistic model for temperature and humidity effects

**Premise:**
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**Below the ERH:** crystal

\[ k_{\text{eff}} = A_{\text{eff}} \exp \left( - \frac{E_{\text{eff}}}{RT} \right) \]

**Above the ERH:** solution

\[ k_{\text{sol}} = \left( \frac{S_{\text{eq}}}{S_0} \right) A_{\text{sol}} \exp \left( - \frac{E_{\text{sol}}}{RT} \right) \]

Morris*, Yinda*, Gamble* et al., unpublished
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**Above the ERH: solution**

\[ k_{\text{sol}} = \frac{[S_{\text{eq}}]}{[S_0]} A_{\text{sol}} \exp \left( -\frac{E_{\text{sol}}}{RT} \right) \]

measured

4 free parameters

Morris*, Yinda*, Gamble* et al., unpublished
SARS-CoV-2 inactivation – mechanistic model fit

**Transient phase, evaporation on-going**

Slopes for all 18 conditions estimated using just 4 free parameters.

**At evaporative equilibrium**

*Morris*, *Yinda*, *Gamble* et al., unpublished
Comparing model predictions to data: in sample

Model predictions for temperature from 0-40°C and relative humidity from 0-100%, overlaid with model-free estimates of virus half-lives.

Morris*, Yinda*, Gamble* et al., unpublished
Comparing model predictions to data: out of sample

Model predictions for temperature from 0-40°C and relative humidity from 0-100%, overlaid with model-free estimates of virus half-lives.

Accurate out-of-sample prediction for three CoV species, above and below ERH.

*Morris, Yinda, Gamble et al., unpublished*
Comparing model predictions to data: out of sample

Model predictions of virus half-lives based on fits to our data only (normalized to a reference point in each study), compared to estimates from literature.

Accurate out-of-sample prediction for five CoV species, from 4-95°C and 30-80% RH.

*Morris*, *Yinda*, *Gamble* et al., unpublished
Environmental effects on SARS-CoV-2 stability

- **Strong dependence** of SARS-CoV-2 stability on temperature and humidity
  - Measured half-lives from ~1 hour to ~1 day
  - Predicted half-lives from half an hour to several weeks

- **Transmission risk greater at cool temperatures, low or high humidities**
  - Meat-packing plants (cold and humid); airplanes (cool and dry)
  - Possible contribution to seasonality

- **Modes of transmission**
  - Similar qualitative patterns reported for *aerosols and smaller droplets*
  - Re-suspension of viruses from surfaces → airborne risk

- **Mechanistic explanation for non-monotonic effect of humidity**

- **Accurate out-of-sample prediction for other human CoV’s**
  → **general mechanisms govern viability of enveloped respiratory viruses**

*Morris*, *Yinda*, *Gamble* et al., unpublished
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Susceptibility of the novel host population
• Case studies: monkeypox and influenza
• COVID-19 and beyond
Major increase in human monkeypox incidence 30 years after smallpox vaccination campaigns cease in the Democratic Republic of Congo

1981-1986

2005-2007

Incidence (per 10,000)

% vaccinated

Incidence (per 10,000)

% vaccinated

0-4 5-9 10-14 15-19 20-24 25-29 >30

0 5 10 15 20 25 30

0 5 10 15 20 25 30

0 5 10 15 20 25 30

0 5 10 15 20 25 30

0 5 10 15 20 25 30

0 5 10 15 20 25 30

Age (years)

Age (years)

Human monkeypox incidence and age distribution rising steadily since 1980.

End of smallpox vaccination ⇒ demographic wave of susceptibility.

Rimoin et al, PNAS (2010)

Lloyd-Smith, Phil Trans B (2013)
Potent protection against H5N1 and H7N9 influenza via childhood hemagglutinin imprinting

Katelyn M. Gostic, Monique Ambrose, Michael Worobey, James O. Lloyd-Smith

Immunological imprinting to first infection with seasonal flu

→ lifelong protection against avian flu viruses from same HA group

Pandemic shifts in seasonal flu subtypes → demographic waves of susceptibility.

Gostic et al, Science (2016)
Implications of pre-existing population immunity

If immunity is structured by age...

... then it alters transmission dynamics and health impacts of a pandemic.

If age-structured immunity is actually structured by birth year...

... then cohort-based waves of susceptibility bring opportunities to forecast emergence risk based on human demography.

Gostic et al, Science (2016)
Pre-existing immunity – COVID-19 and beyond

Conclusions from monkeypox and influenza case studies:

• ‘Novel’ virus, but human population is partially immune
• Cross-immunity from broader community of pathogens
• Influences outbreak dynamics and health impacts
• Strong age patterns in susceptibility to disease
• ... actually driven by birth-year → demographic waves

Statistically impossible to discern age-based vs birthyear-based patterns, when all data comes from 2020.
But available evidence suggests it’s age-based.

Ingredients for birthyear-based patterns and demographic waves of risk:
• Past shifts in circulating strains, giving rise to shifts in cross-immunity.
• Past shifts in vaccination practices.
e.g. rinderpest, polio, pneumococcus, measles, dengue, etc.
Summary

New techniques to estimate human-to-human transmissibility in previously intractable settings.

Steps toward unpacking virological components of transmission, using models to reveal general principles.

Population immunity can be important for ‘novel’ pathogens, shaping outbreak dynamics and emergence risk.
Next frontiers and discussion points

**Superspreading** is back...
- Renewed discussion of how to predict (people or settings) to benefit from efficient targeted control. How much of variance is predictable?
- Why are emerging coronavirus so prone to superspreading?

**Unpacking transmission** by modeling lab experiments
- Huge potential for synergy and cross-fertilization between fields
- Aim to make strong predictions and test them
  - e.g. predict outcomes of transmission experiments

Key knowledge gaps related to **infectious dose and route**
- What is infectious dose (via different routes of exposure) for SARS-CoV-2?
- How do dose and route of exposure shape the course of infection?
- What is relative importance of different transmission routes in the field?

Measuring and understanding **population immunity** to novel pathogens
- Next-generation immunological tools (VirScan etc)
- Does existing immunity block infection or disease? Onward transmission?
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[FOGARTY]
Projecting the impact of rising susceptibility to MPX

Vaccination surveys + Human demography data + Estimate of $R_0$

Proportion vaccinated

Effective Reproductive Number ($R$)

$R_0$ estimate and confidence interval

<table>
<thead>
<tr>
<th>Year</th>
<th>Proportion vaccinated</th>
<th>Effective Reproductive Number ($R$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1970</td>
<td>1</td>
<td>0.2</td>
</tr>
<tr>
<td>1980</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>1990</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>2000</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>2010</td>
<td>0.2</td>
<td>0.2</td>
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<td>0.2</td>
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<tr>
<td>2050</td>
<td></td>
<td>0.2</td>
</tr>
<tr>
<td>2060</td>
<td></td>
<td>0.2</td>
</tr>
</tbody>
</table>
Puzzle: Age distributions of H5N1 vs H7N9 flu cases

Previous explanations:
- different exposure to poultry? *Cowling et al, Eurosurv 2013*
- pre-existing immunity to N1? *Kucharski et al, Epid Inf 2015*
- differential severity by age, leading to ascertainment bias? *Qin et al, CID 2015*

Proposed explanation: **HA imprinting**: immune system imprints on the HA group of your first influenza infection

→ lifelong (partial) protection against other subtypes from same group.

*Gostic et al, Science (2016)*
Reconstructed exposure histories

![Timeline diagram showing reconstructed exposure histories for influenza A strains H1N1, H2N2, and H3N2.]

Initial exposures to influenza A, by birth year – China 2015

- **Born before 1968**: First exposed to group 1
- **Born after 1968**: Likely 1st exposed to group 2

Legend:
- Group 1 HA
- Group 2 HA
- Naïve

Gostic et al, Science (2016)
Risk of severe infection or death by birth year

H7N9

Incidence
Mortality
A priori prediction

Cases
Birth year

Excess cases
Birth year

H5N1

Incidence
Mortality
A priori prediction

Cases
Birth year

Excess cases
Birth year

A priori prediction

H7N9

H5N1
Implications for pandemic risk assessment

Consider **hypothetical** strains of H5 and H7 with $R_0 > 1$ in humans.

Combine: age-susceptibility profiles from this work

+ age-mixing patterns from POLYMOD study.

→ **Project severe infection rate by age**

for H5 or H7 pandemics occurring in UK in 2015.

---

**Fraction of individuals in age group with severe infection**

- H5 pandemic
- H7 pandemic
- Either pandemic, without HA imprinting

**Gostic et al (2016) Science**
Implications for pandemic risk assessment

First childhood exposure acts like vaccination against other HA subtypes in the same HA group.

→ Prolonged dominance by one HA group will shape patterns of population immunity, and hence emergence risks.

**Scenario: H2 pandemic replaces current seasonal strains**

Zoonotic strain from mismatched group can go from subcritical to supercritical, solely due to generational shifts in HA imprinting.

Environmental effects on SARS-CoV-2 stability

- Virus stability is known to be affected by temperature and humidity

Morris*, Yinda*, Gamble* et al., unpublished
SARS-CoV-2 inactivation - mechanistic model fit

At evaporative equilibrium

Morris*, Yinda*, Gamble* et al., unpublished
SARS-CoV-2 inactivation - mechanistic model fit

**Transient phase**

<table>
<thead>
<tr>
<th>Temperature (°C)</th>
<th>10</th>
<th>22</th>
<th>27</th>
</tr>
</thead>
</table>

| Relative humidity (%) | 40 | 65 | 85 |

Virus titer (TCID\(_{50}\)/mL media)

Time (hrs)

Morris*, Yinda*, Gamble* et al., unpublished
SARS-CoV-2 inactivation – model-free regression fit

At evaporative equilibrium

Morris*, Yinda*, Gamble* et al., unpublished
How effective is symptom and risk screening at detecting COVID-19 infected people?
Mathematical model to estimate effectiveness of screening

- For symptoms and/or risk of exposure
- At departure and/or arrival
Mathematical model to estimate effectiveness of screening

- For symptoms and/or risk of exposure
- At departure and/or arrival
- Or at any single point in time (entering store, workplace, etc)
Ability to detect cases depends on time since exposure, due to incubation period before people show symptoms.
Ability to detect cases depends on time since exposure, due to **incubation period** before people show symptoms.

Overall performance depends on key unknowns – especially % **subclinical**.
COVID-19 – Efficacy of symptom and risk screening

• Mathematical model integrating all factors that determine screening success
  • Incubation period, % with symptoms, % with known exposure, etc.

• Captures knowledge and uncertainty about COVID-19 as of mid-February

Dot shows average fraction detected. Line and shape show the range.

Gostic et al. 2020, eLife
COVID-19 – Efficacy of symptom and risk screening

- Mathematical model integrating **all factors that determine screening success**
  - *Incubation period, % with symptoms, % with known exposure, etc.*
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Gostic et al. 2020, *eLife*
COVID-19 – Efficacy of symptom and risk screening

- Mathematical model integrating **all factors that determine screening success**
  - *Incubation period, % with symptoms, % with known exposure, etc.*
- Captures **knowledge and uncertainty** about COVID-19 as of mid-February

**Symptom screening will detect less than half** of infected people, maybe as few as **1 in 10 → Not a viable standalone strategy.**

Gostic et al. 2020, *eLife*
COVID-19 – From virologic traits to transmission risk

PPE is essential! But what about the mask shortage?

- Tested four methods for decontamination and reuse of N95 masks
  - Heat, UV-C radiation, ethanol, vaporized hydrogen peroxide
- Measured killing rate of virus, and impacts on mask performance

Fischer et al., 2020, *Emerg Inf Dis*
PPE is essential! But what about the mask shortage?

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- Measured **killing rate of virus, and impacts on mask performance**

![Graph showing kill rate (per virus per min) after decontamination.](image)

**FAIL**

**PASS**

1 round

Mask performance after decontamination

Fischer et al., in revision for *EID*
PPE is essential! But what about the mask shortage?

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  - Heat, UV-C radiation, ethanol, vaporized hydrogen peroxide
- Measured killing rate of virus, and impacts on mask performance

→ Vaporized hydrogen peroxide kills virus fast, and preserves mask function

Fischer et al., 2020, *Emerging Infectious Diseases*