

2019 Novel Coronavirus Global Research and Innovation Forum:

Towards a Research Roadmap

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<https://www.glopid-r.org> @GloPID_R



Background

- WHO's R&D Blueprint has been activated since early January 2020, providing transparent and coordinated information sharing on research starting before the causal agent was identified.
- R&D Blueprint works closely with GLOPID-R



Background

- GLOPID-R an international network of research funding organizations
- “facilitate, accelerate and deepen collaboration among research funders on emerging diseases”:
- to strengthen global research **preparedness** between crises.
 - to **respond** rapidly and effectively to significant infectious disease outbreaks.



28 Members and 2 observers



Background

- Many unknowns including:
 - disease and its optimal management
 - virus reservoirs (the origin?)
 - virus evolution
 - transmission and epidemiology
- Urgent need to develop safe and effective countermeasures that can be available, accessible and suitable for use in populations most in need

**Research is an important integral component
of the response**



Global research response: multi-sectoral and interdisciplinary with cross-border collaborations;
partnerships across professional disciplines,
across sectors and across borders



Global international research: core concepts

- **Focus:** Have common goals and minimum common program
- **Values:** Understand others organizational culture & underlying societal norms
- **Equity:** Mutual respect and openness
- **Benefit:** Communities and/or organizations
- **Communication:** open, honest and unambiguous
- **Leadership:** development and careful planning



Datasharing to:

- reduce the duplication of work
- provide a clearer picture of epidemiology and pathology

Principles for datasharing: Timely – Ethical – Accessible
– Transparent – Equitable – Fairness - Quality



Meeting Purpose

- To enable identification of key knowledge gaps and research priorities, and thereby accelerate the generation of critical scientific information and the most needed medical products to contribute to the control the 2019-nCoV emergency.

With researchers from multiple specialties, funders, public health, regulatory experts, ethicists



Expected Outcome

- A research roadmap with clearly defined priorities and governance framework addressing all of the thematic areas outlined in the agenda

Format

- Review of epidemiological situation, and overviews of each thematic area this morning
- Parallel sessions this afternoon
- Tomorrow:
 - Developing a coherent research roadmap
 - Governance Framework

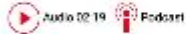
Note confidential data may be presented

- And confidentiality of such data must be respected
- All those taking part whether in person or remotely must have signed the confidentiality agreement

L'épidémie de fièvre de Lassa connaît une évolution inquiétante au Nigeria



Publié le 08/07/2020 - 00:05



Au Nigeria, le personnel médical doit s'équiper d'une protection spécifique pour soigner les malades atteints de Lassa (R). (Fransjo Limes-Ferrel)

Lassa epidemic in Nigeria

Home - Africa - Crimean-Congo hemorrhagic fever: 7 deaths in Mali village

Crimean-Congo hemorrhagic fever: 7 deaths in Mali village

by NEWS DESK

February 7, 2020

Africa, Headlines

No Comments



IQ test - What is your IQ?

By NewsDesk @infectiousdiseasews

Government officials in the government of Mopti are reporting seven human Crimean-Congo hemorrhagic fever (CCHF) deaths, according to Swiss Info report (computer translated).



In the village of Samon, 14 cases were reported. Crimean-Congo hemorrhagic fever (CCHF) is caused by the Crimean-Congo hemorrhagic fever tick-borne virus (Nairovirus) of the virus causes severe viral hemorrhagic fever with a fatality rate of 10-40%.

Subscribe to Outbreak News 7

Animals become infected by the bit remains in their blood stream for allowing the tick animal-tick cycle. Although a number of tick genera a CCHF virus, ticks of the genus Hyalomma

The CCHF virus is transmitted in p

CCHF epidemic in Mali

New cases of Ebola confirmed in DR Congo



NENTREH (S)

FULLLOK

Following the latest outbreak in NEWS

Support Our African Journalists SUBSCRIBE



Ebola epidemic in DRC

Thank you

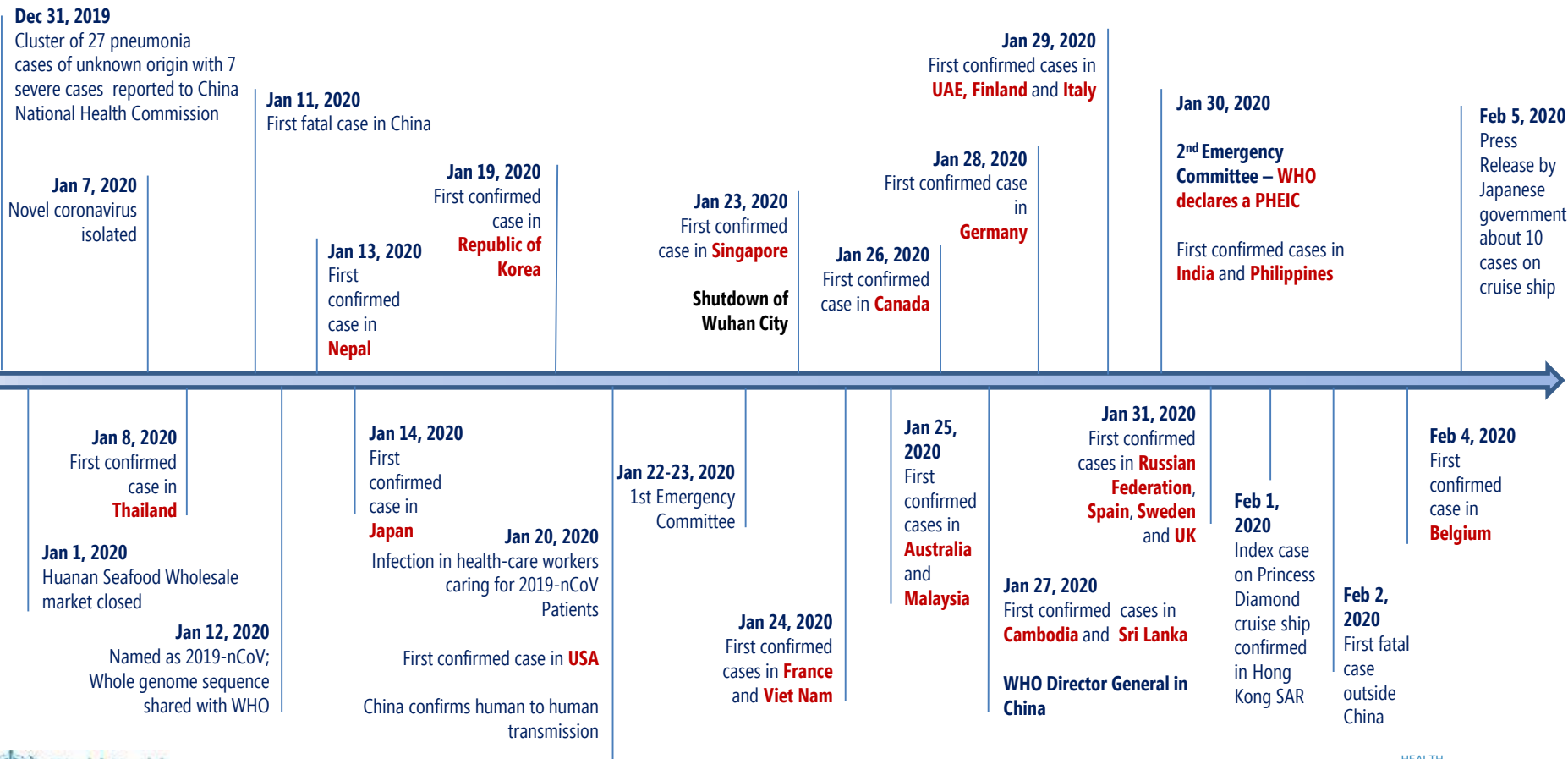
Together, we can make a difference for those suffering from or at risk of 2019-nCoV infection



Update on 2019-nCoV

11 February 2020

Evolution of the 2019-nCoV outbreak (31 December 2019 – 10 February 2020)



Current Situation (as of 11 Feb, 6am Geneva time)

Updates from last 24 hours

China:

- 2,484 new confirmed cases: 84%, 2,097 cases from Hubei
- 849 new severe cases and 108 deaths: Hubei(103), Beijing(1), Tianjin(1), Heilongjiang(1), Anhui(1), Henan(1))
- 3,536 new suspected cases

Outside China:

- 74 new confirmed cases: International conveyance (Japan)(65), The United Kingdom(4), Singapore(2), Viet Nam(1), United Arab Emirates(1), Republic of Korea(1)

Between 31 Dec 2019 - 11 Feb 2020

In total, 43,101 confirmed cases including 1,018 deaths globally

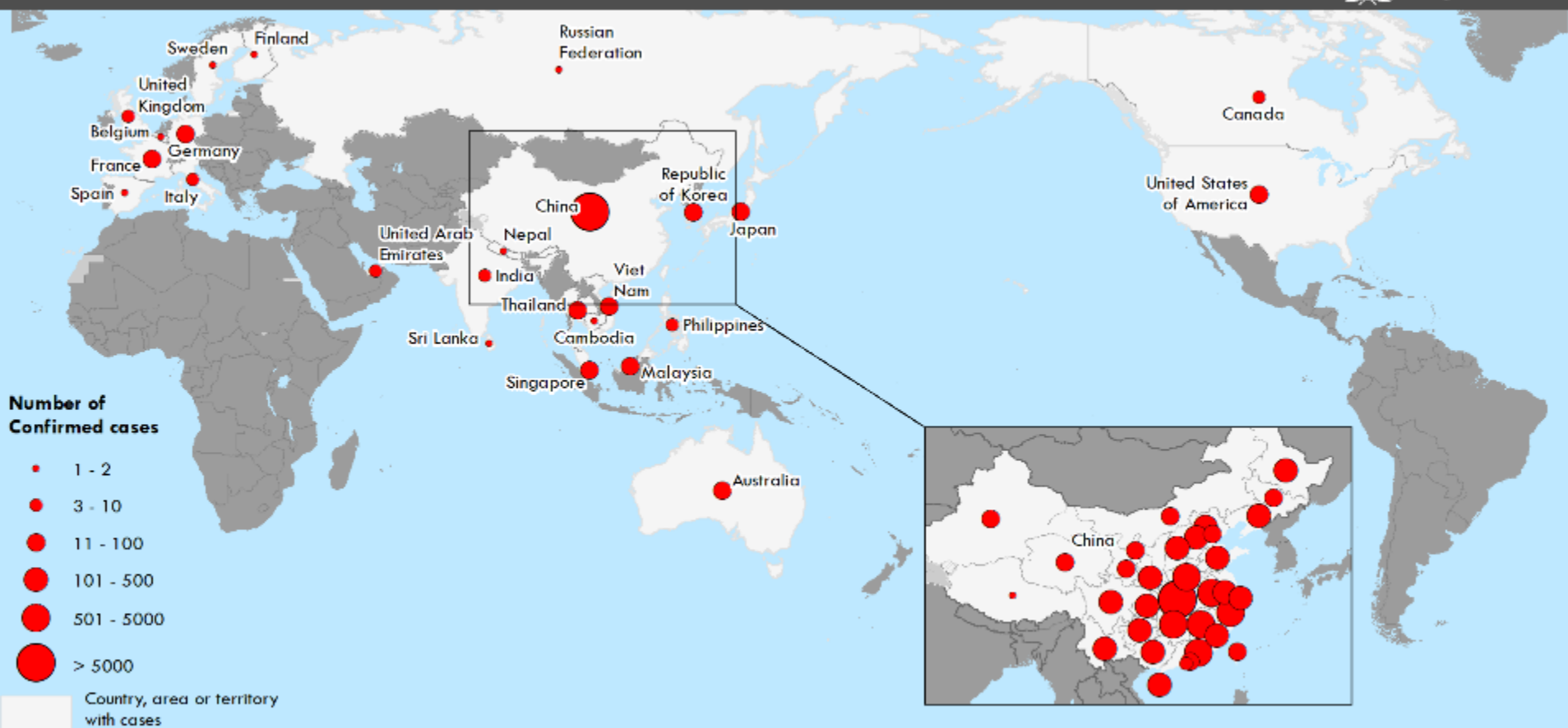
China

- 42,708 confirmed cases
- 7,333 severe cases
- 1,017 deaths: Hubei(974), Heilongjiang(8), Henan(7), Anhui(4), Beijing(3), Hainan(3), Tianjin(2), Hebei(2), Chongqing(2), Gansu(2), Jilin(1), Shanghai(1), Jiangxi(1), Shandong(1), Hunan(1), Guangdong(1), Guangxi(1), Sichuan(1), Guizhou(1), Hong Kong SAR(1)

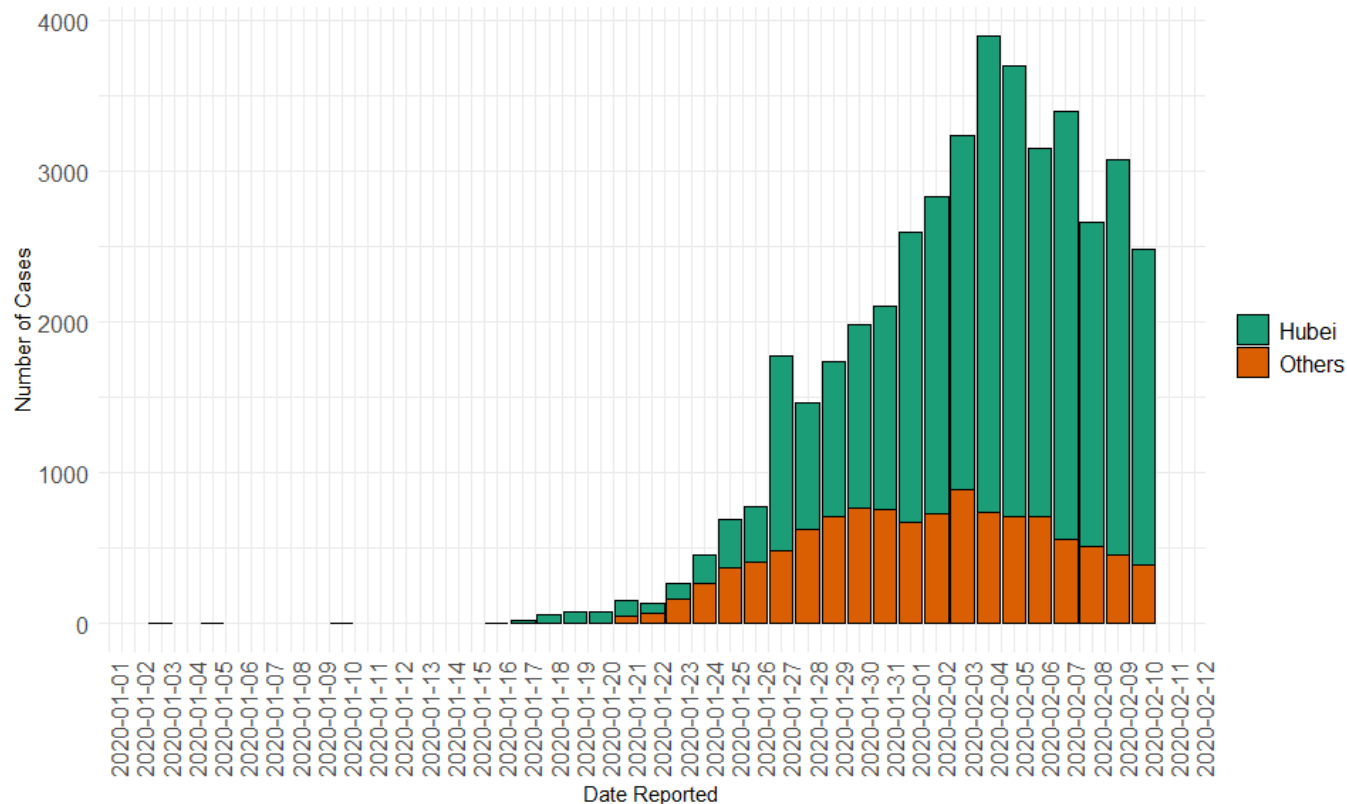
Outside China

- 393 cases from 24 countries
- 1 death

Distribution of 2019-nCoV cases as of 10 February 2020

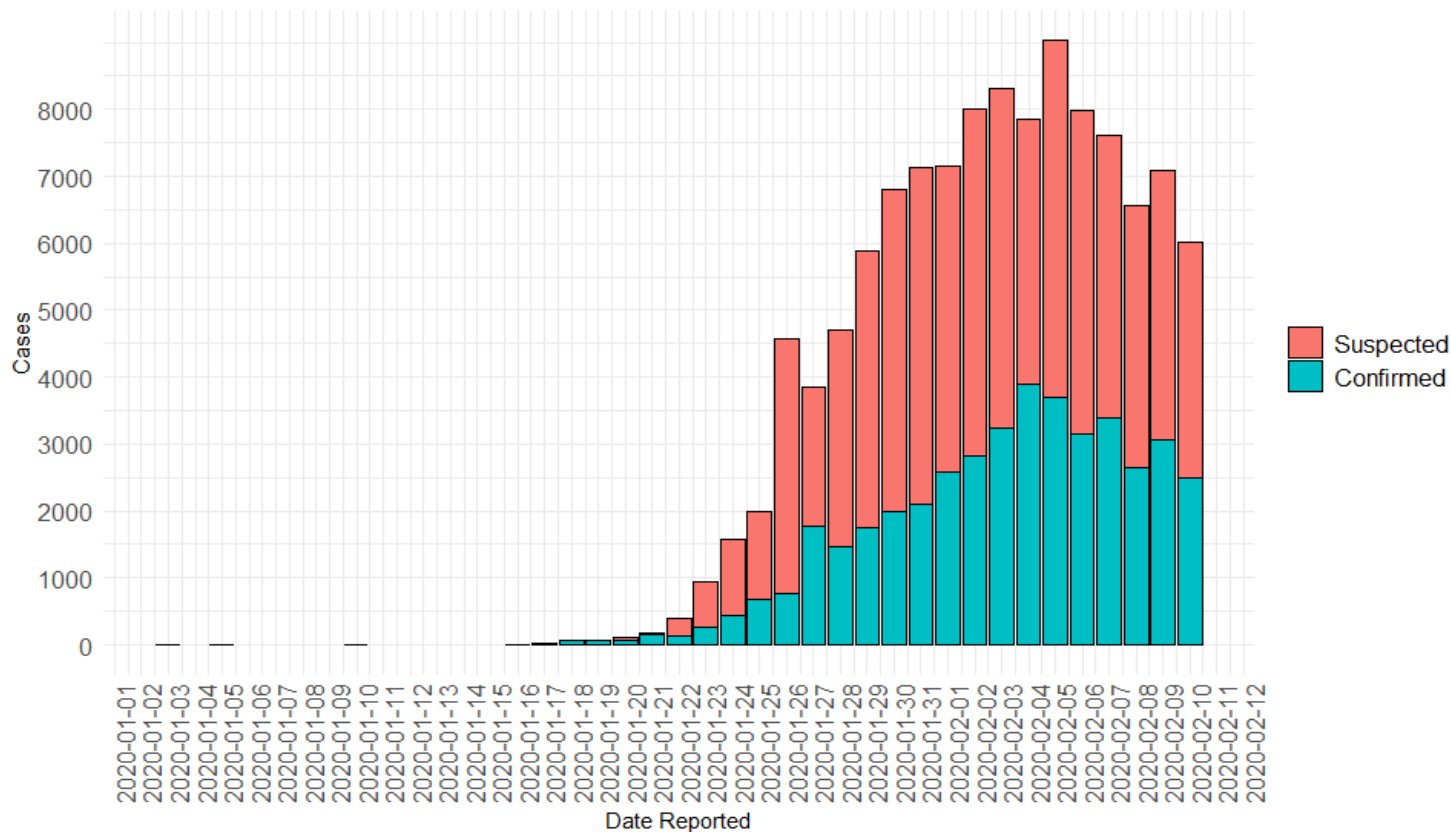


Number of confirmed cases in China by day of report (Hubei vs. Other Provinces)



(based on the data from China CDC)

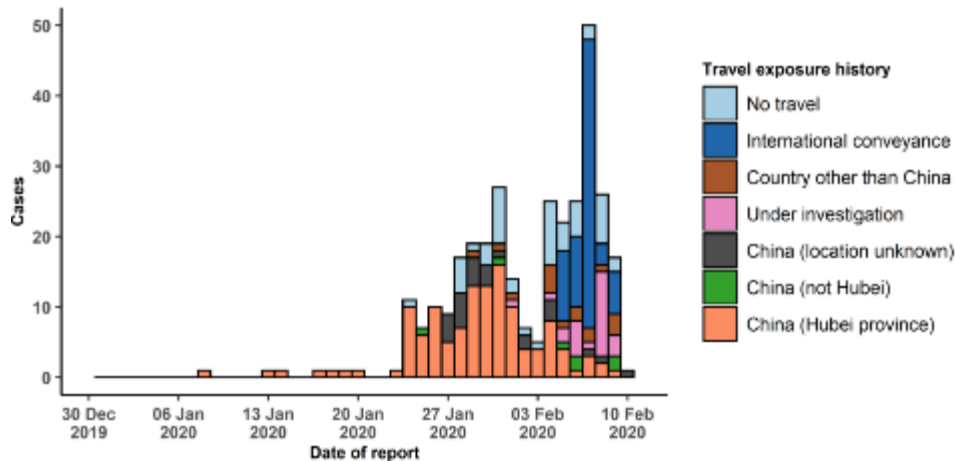
Number of reported confirmed and suspected cases in China by day of report



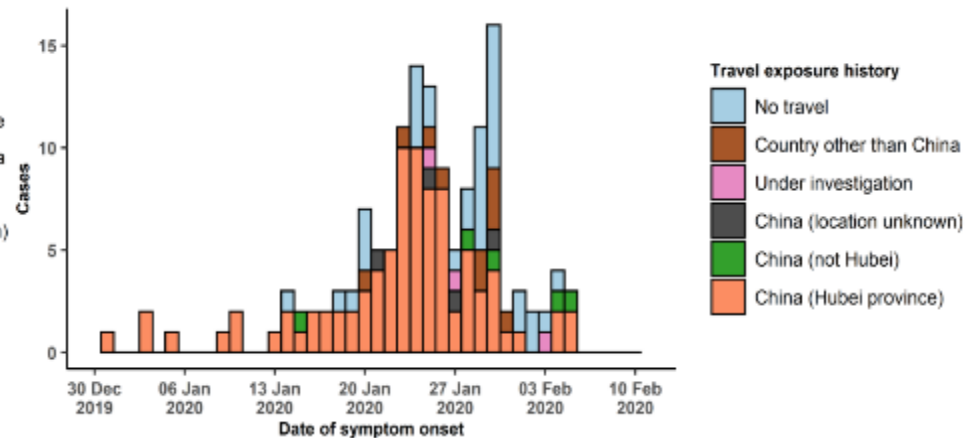
(based on the data from China CDC)

Number of Cases of 2019-nCoV Reported Outside of China As of 10 February

Confirmed cases of 2019-nCoV identified outside of China, by date of reporting and travel history (n=319)



Confirmed cases of 2019-nCoV identified outside of China, by date of onset of symptoms and travel history (n=144)*



*16/319 cases detected while asymptomatic; Information on date of onset not available for remaining cases

Severity of disease among reported 2019-nCoV patients

- Patients present with fever, cough, shortness of breath, myalgia, confusion, headache
- Severity ranges from mild to severe disease resulting in death
 - As of 10 Feb 7,333 patients reported as severe (17%) and an additional 1,018 people (2%) have died
- Fatal cases in China strongly associated with older age (>60 years old); comorbidities common in older patients, may not be an independent risk factor
 - Cause of death due to progressive respiratory and multi-organ failure
 - Most deaths occur after prolonged course (7-10 days)
 - 55% of the patients reported as severe have recovered
- True case-fatality ratio difficult to assess, denominator (number of infections) unknown

Transmission features

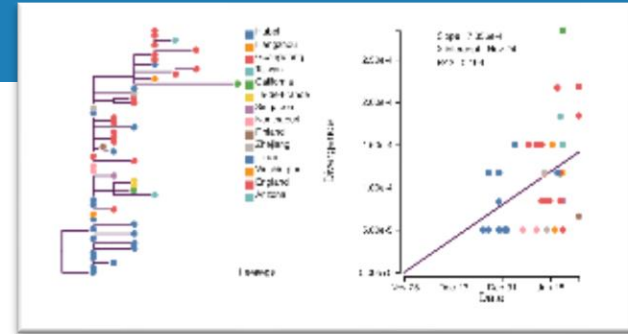
- **2019-nCoV is a zoonotic virus; supported by:**

- Epidemiologic evidence of exposures of some initial cases
- Results of environmental sampling in Huanan Seafood and live animal market
- Early phylogenetic results suggest initial human infection in ongoing human-to-human transmission

➔ Animal source not yet identified; spillover events could continue

- **Human-to-human transmission**

- Transmission via droplet, contact, fomites
 - Occurring amongst close contacts, including family members and HCWs
 - 1 example of health-care associated outbreak in Wuhan (involving 15 HCW), HCW infections in other cities in China, in France
 - Detailed exposure histories and investigations are needed to understand frequency and significance of transmission from asymptomatic PCR positive people; not known to be drivers of transmission for other coronaviruses
- Transmission parameter estimates
 - Estimates of R_0 ranging from 1.4-4.9 in China
 - Incubation period estimated range 1-12.5 days, median 5-6 days (WHO guidance includes 14 days)
 - Limited H2H transmission in 10 countries outside of China



54 full genomes available

WHO Risk Assessment

Overall risk		
National	Regional	Global
Very High	High	High

- Likelihood of spread
 - Ongoing human-to-human transmission
 - Confirmed identified in 31 provincial level administrative areas (10 with >100 cases)
 - Majority of cases exported outside China have been epidemiologically linked to Wuhan
 - Human-to-human transmission documented in other countries
 - Source of outbreak remains unknown
 - Disaggregated data is needed to better understand the epidemiology
- Potential impact to human health
 - Can cause severe disease and fatalities
 - Severity is not fully understood
 - Transmission from asymptomatic cases
- Likelihood of insufficient control capacities
 - China has implemented major control measures
 - Currently affected countries have strong public health systems
 - Some countries may be less prepared to manage cases

Priorities for stopping transmission and mitigating the impact of 2019-nCoV globally

- **Limit human-to-human transmission**
 - Reduce secondary infections among close contacts and health care workers
 - Prevent transmission amplification and super spreading events
 - Prevent further international spread
- **Identify, isolate and care for patients early**
 - Equip countries to detect, isolate and care for infected patients
 - Provide optimized care
- **Reduce transmission from animal source**
 - Identify animal source(s) and limit exposure
- **Address critical unknowns**
 - Clinical severity, extent of transmission and infection, treatment options, diagnostics, therapeutics and vaccines
- **Communicate critical risk and event information to all communities & counter misinformation**
- **Minimize social and economic impact through multisectoral partnerships**

WHO technical guidance to support countries

Surveillance and case definitions

Laboratory testing

Clinical management

Infection prevention and control

Home care

Risk communication & community engagement

Country readiness

Disease commodity package

Reducing risk of transmission from animals

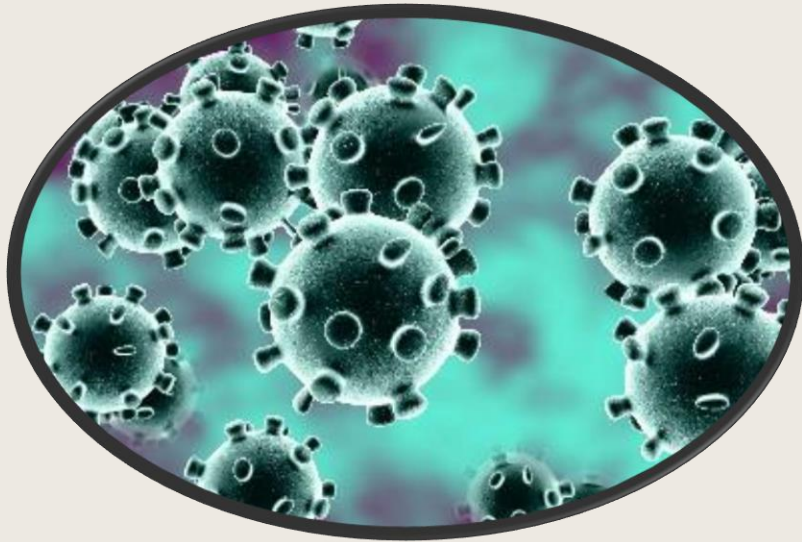
Use of masks

Strategic response plan: Accelerating priority research and innovation

- Address crucial unknowns regarding clinical severity extent of transmission and infection, treatment options
- Enhance global coordination of all relevant R&D stakeholders through existing mechanisms
- Support a clear and transparent global research and innovation priority setting process
- Build common platforms for standardized processes, protocols and tools, as well as for sharing specimens, data, and information



2019 novel Coronavirus Global research and innovation forum: *towards a research roadmap*



R&D Blueprint

Powering research
to prevent epidemics

Overview of state of the art and outline of key knowledge gaps

- **State of the art**
- **Knowledge gaps**
- **Ongoing research efforts**

Overview of state of the art and outline of key knowledge gaps – State of the art

- In-house RT-PCR detection in place, deployment ongoing (current focus: Africa)
- Ready-to-use formulations on research use only basis available, *in vitro* diagnostic-qualified products in the pipeline
- Virus isolation capacities available in reference centers
- Generic sequencing capacities widely available
- Virus isolates available under minimal material transfer agreements
- **In all of these provisions: severe bottlenecks in logistics**

Overview of state of the art and outline of key knowledge gaps – Knowledge gaps: clinical virus detection

- Compartments of replication
- Prognostic information from viral load or viral load trajectories
- Prognostic information from immuno-markers
- Infectivity surrogates, discharge criteria

- Treatment-related monitoring
 - Escape mutants (in-vitro, empirical)
 - Geno-to-pheno approaches

- Phenotypic change (geno to pheno)
- Diagnostic drift: PCR assay compatibility changing over time

Overview of state of the art and outline of key knowledge gaps – Knowledge gaps: immunity and immune diagnostics

- Strength and duration of immunity
- Influence of pre-existing immunity against heterologous human coronaviruses
- Reflection of immunity by antibody tests
- Reflection of immunity by cell-level surrogates (Elispot etc.)
- Utility of innate immunity testing in patients
- Value of advanced affinity assays (e.g., whole proteome arrays)
- Sero-specificity and costimulation in serological diagnostics
- Technical gaps: simple IFA, differential IFA, ELISA, Neutralization assays, Neutralization assay surrogates including pseudotypes and competitive ELISA

Overview of state of the art and outline of key knowledge gaps – Knowledge gaps: tools for infection control

- Virus stability (physical, chemical inactivation)
- Surrogate viruses for stability studies (BCoV, MHV, etc.)
- Infectivity of RNA

- Technical gaps: Infectivity assays (cell culture models, animal models); point of care tests

Overview of state of the art and outline of key knowledge gaps – Knowledge gaps: clinical processes

- High throughput and automation of PCR detection
 - Point of care testing
 - Respiratory pathogens multiplex detection
 - Devices related to prognostic markers
 - Digital solutions for field lab assistance
-
- Bedside and lab-based sequencing approaches

Overview of state of the art and outline of key knowledge gaps – Ongoing research efforts

- Descriptive patient-centered studies based on individual cases or opportunity-driven cohorts
- Implementation-related work
 - Validation of in-house protocols
 - Validation of kits
 - Logistics
 - Reference laboratory services
- Provision of virus and reference material (European Virus Archive-Global)

Overview of state of the art and outline of key knowledge gaps – **Conclusions**

Key areas of focus/considerations for research on the virus

1. What is the location and duration of viral replication and shedding; what are implications for clinical management?
2. How best to characterize transmissibility and infectivity in laboratory environments?
3. What is the role of ongoing genome sequencing for outbreak management and development/monitoring of countermeasures
4. What are the key uses for immunodiagnostics/serology
5. How do we maximize impact of research in this area taking into account timeframes and feasibility?

Overview of state of the art and outline of key knowledge gaps

- State of the art
- Knowledge gaps
- Ongoing research efforts

Thematic area 2

Animal and environmental research on the virus origin, and management measures at the human-animal interface

Overview of state of the art and outline of key knowledge gaps – State of the art

- 2019-nCoV **96.2%** full genome identity with a clade 2b β -CoV from *Rhinolophus affinis* bat in Yunnan, China.
- All clade 2b CoVs found in bats (exc. SARS-CoV which may have evolved from a bat SARSr-CoV via interm hosts)
- *Rhinolophus* spp. abundant & diverse in S. China, and across Asia, the Middle East, Africa and Europe.
- >500 CoVs identified in bats in China, incl. SADS-CoV, SARSr-CoVs. Estimates of likely unknown CoV diversity in bats reach >5,000
- Southwest China and neighboring countries: likely center of evolutionary diversification of clade 2b CoVs (Latinne *et al.* in review).

Overview of state of the art and outline of key knowledge gaps – State of the art

- High proportion of 1st & 2nd gen. human cases to the Huanan Seafood Wholesale Market in Wuhan.
- Route of spillover from bats to humans unclear, and may involve domesticated mammals, farmed or hunted wildlife (e.g. civets, cf. SARS-CoV)
- Bats are rare in markets in S. China, but hunted widely and sold directly to restaurants for food (Li et al. 2019)
- 2.9% bat-CoV seroprevalence in small sample of rural Yunnan people: non-market exposure to bat-CoVs is common (Wang et al. 2018).
- Extrapolation of human seroprevalence across *Rhinolophus* spp. hotspots in SE Asia: largescale exposure to bat CoVs in the community (multiple million people)

Overview of state of the art and outline of key knowledge gaps – Knowledge gaps

- Species of origin of the virus
- Geographic origin (endemic vs imported via trade, etc.)
- Prevalence of the virus in various species of animals (host and possible intermediate host)
- Mode of transmission to humans
- Risk reduction strategies for animal to human transmission

Overview of state of the art and outline of key knowledge gaps – Ongoing research efforts

- Investigations into genetic relatedness to other animals CoV's
- Investigations into host susceptibility (in-vitro, receptor binding studies, etc.)

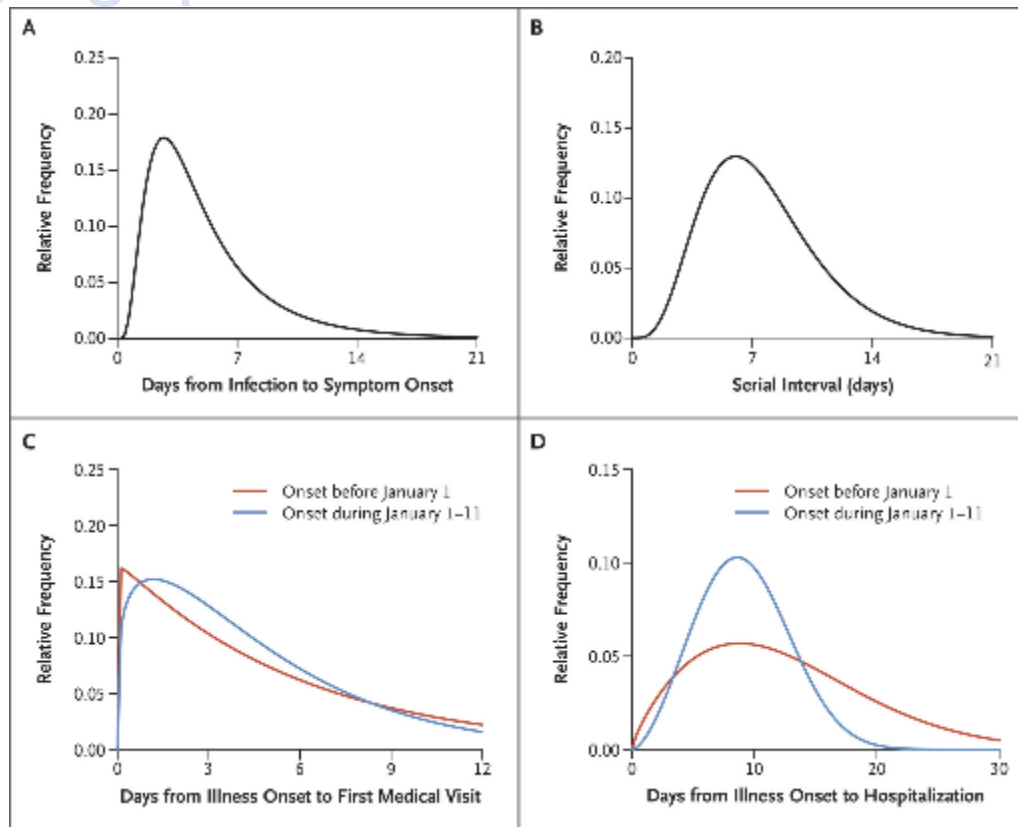
Overview of state of the art and outline of key knowledge gaps

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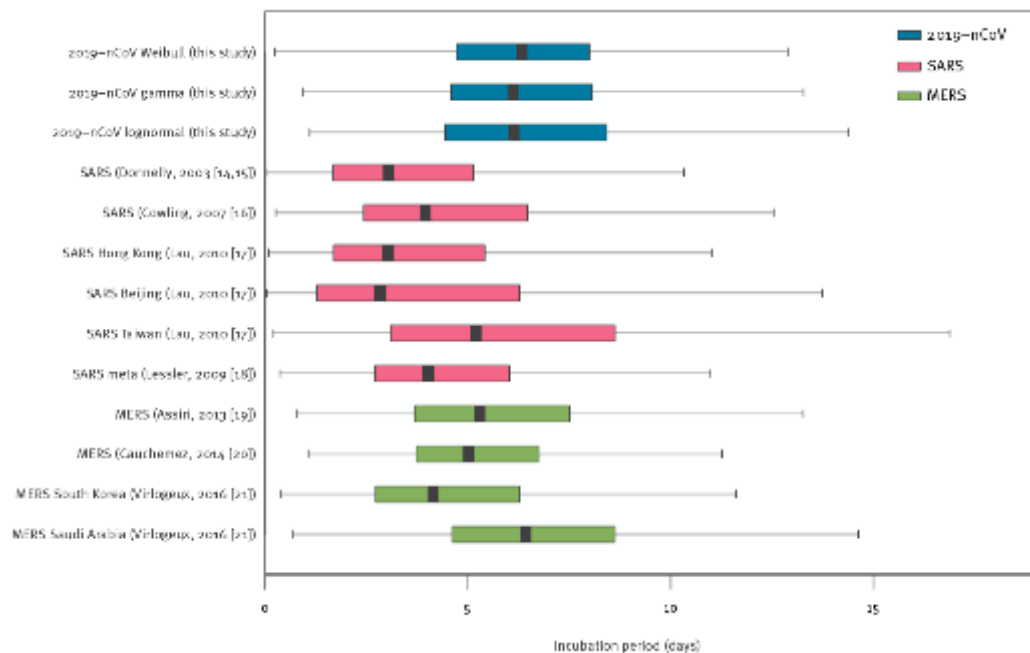
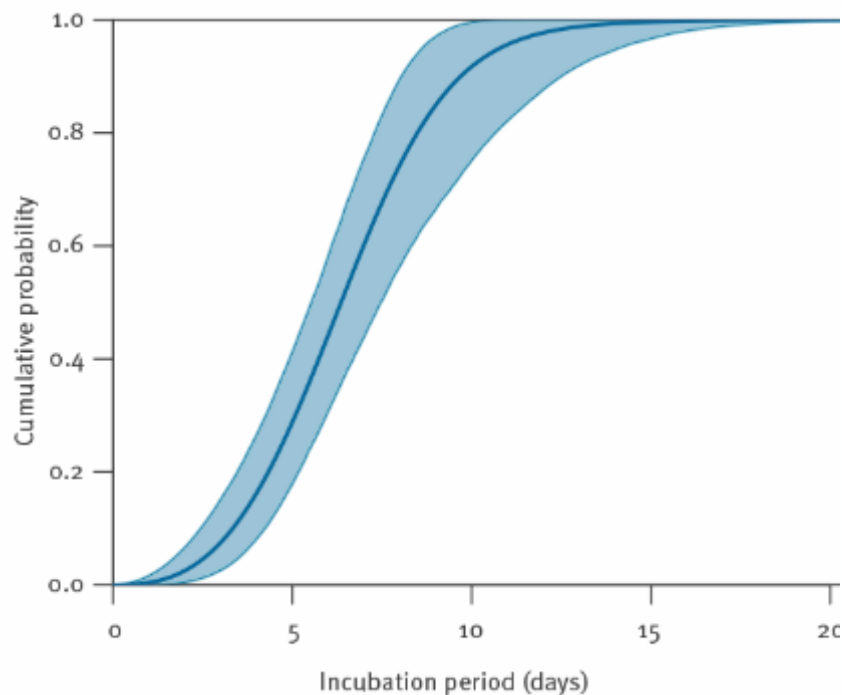
List of questions to be addressed

1. What is the **transmissibility** in different epicentres over time, including the R_0/R_t , serial interval, modes of transmission, environmental factors etc.?
2. What is the **severity** of disease, different levels of fatality risk stratified by baseline risk groups?
3. Who is **susceptible**, are children infected/infective, do all infections result in neutralizing immunity?
4. What is the **impact of interventions**, such as non-pharmaceutical interventions, mobility restrictions, social distancing, etc?

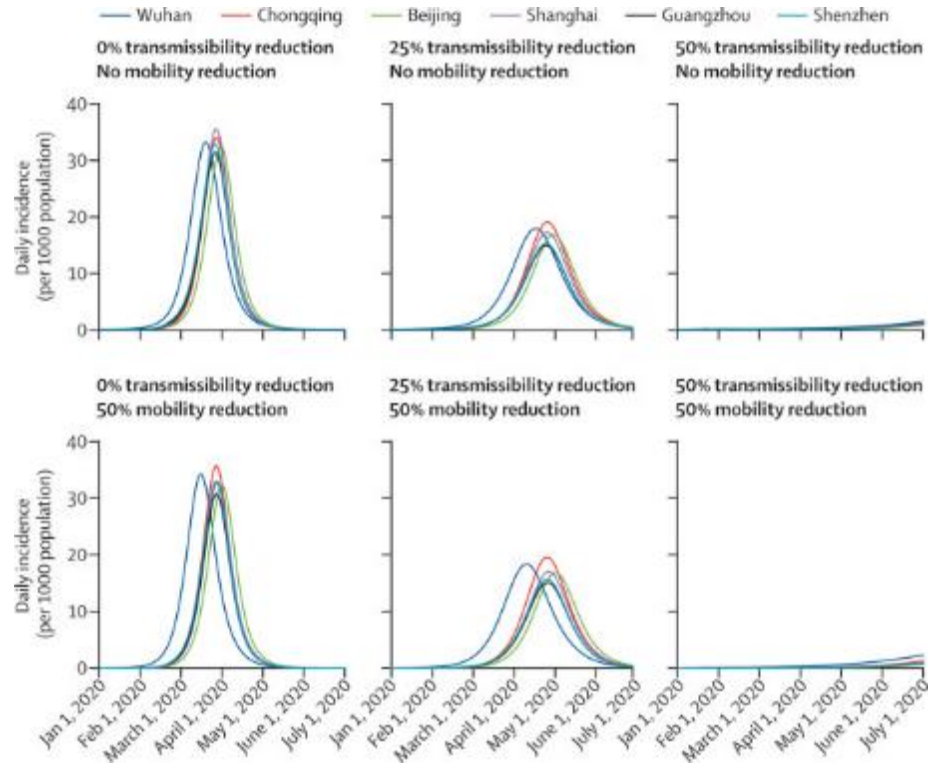
Overview of state of the art and outline of key knowledge gaps – State of the art



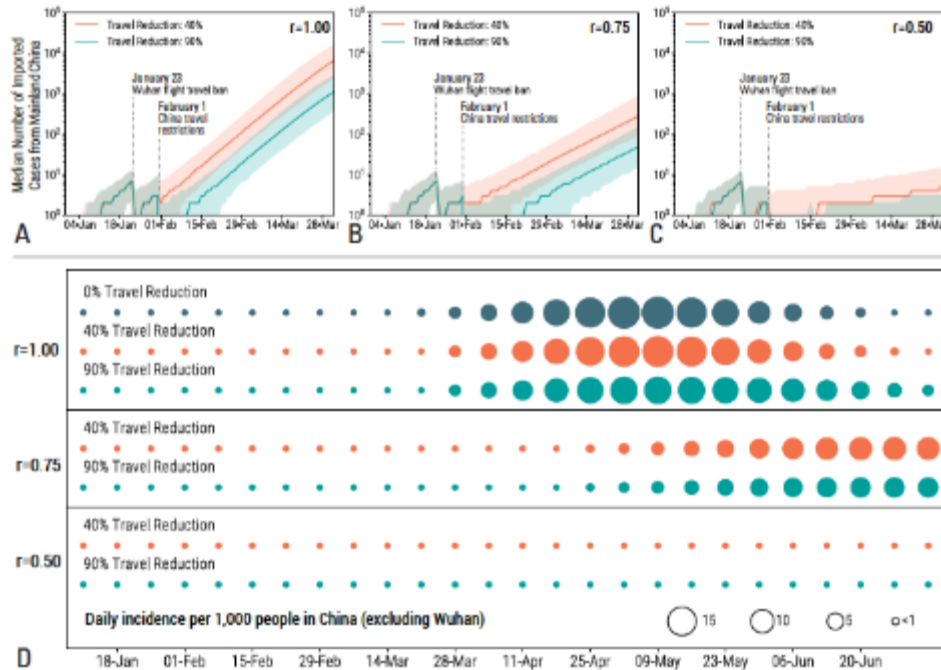
Overview of state of the art and outline of key knowledge gaps – State of the art



Overview of state of the art and outline of key knowledge gaps – State of the art

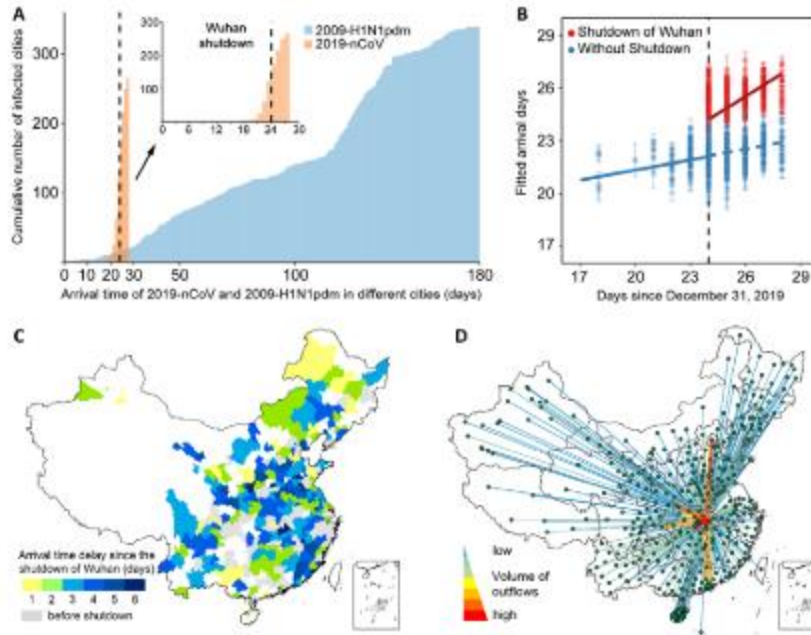


Overview of state of the art and outline of key knowledge gaps – State of the art



The model shows that as of January 23, most Chinese cities had already received a considerable number of infected cases, and the travel quarantine delays the overall epidemic progression by only 3 to 5 days. The travel quarantine has a more marked effect at the international scale, where we estimate the number of case importations to be reduced by 80% until the end of February. Modeling results also indicate that sustained 90% travel restrictions to and from Mainland China only modestly affect the epidemic trajectory unless combined with a 50% or higher reduction of transmission in the community.

Overview of state of the art and outline of key knowledge gaps – State of the art

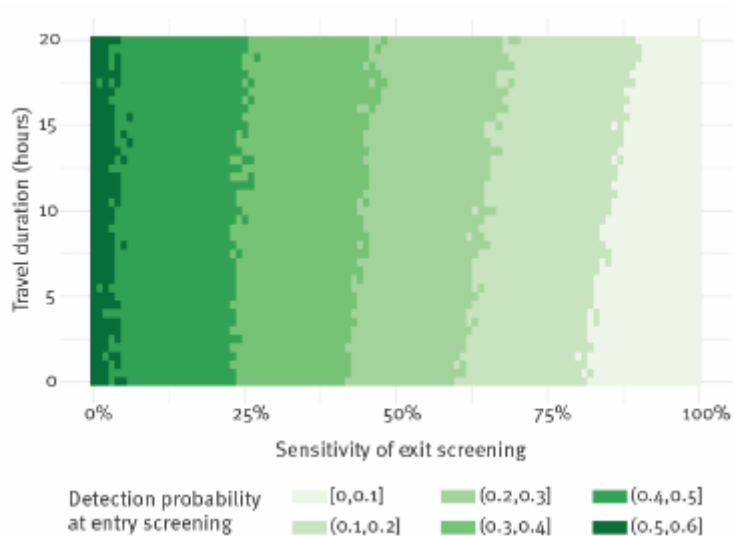


... the travel ban slowed the dispersal of nCoV from Wuhan to other cities in China by 2.91 days (95% CI: 2.54-3.29)

Tian et al 2020 preprint available at <http://dx.doi.org/10.1101/2020.01.30.20019844>

Overview of state of the art and outline of key knowledge gaps – State of the art

Quilty et al *Euro Surveill* 2020



...46% (95% CI: 36 to 58) of infected travellers would not be detected...Airport screening is unlikely to detect a sufficient proportion of 2019-nCoV infected travellers to avoid entry of infected travellers.

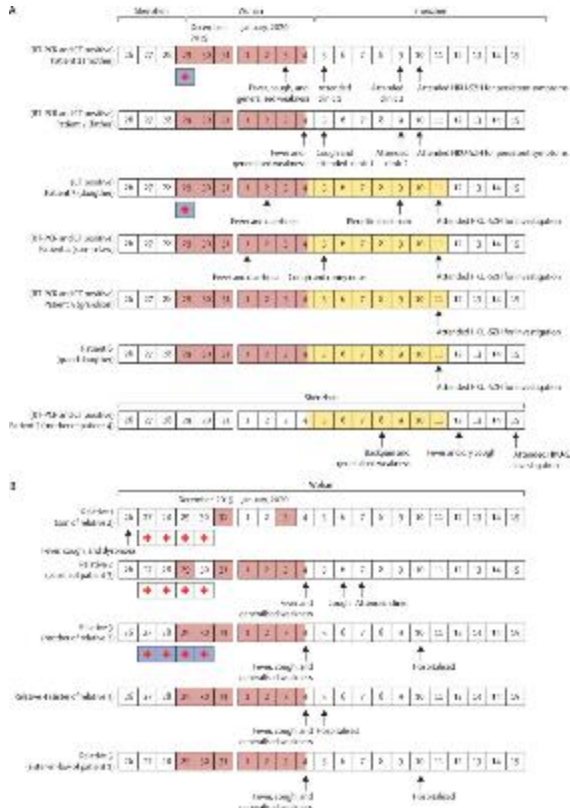
Cowling et al. *BMC ID* 2010

Screening approaches used	n (%)	Median interval, days (inter-quartile range)	Mean interval, days	Mean difference in intervals compared to no screening (95% CI)*
No screening	5 (19%)	22 (0, 22)	14	
1- Medical checks before disembarkation	2 (8%)	21 (14, 28)	21	7 (-14, 30)
2- Health declaration forms	11 (42%)	22 (13, 34)	23	9 (-4, 24)
3- Symptom screening	13 (50%)	33 (7, 41)	26	12 (-2, 27)
4- Thermal scanners	13 (50%)	22 (7, 33)	21	7 (-6, 23)
2 OR 3 OR 4	21 (81%)	22 (7, 35)	23	9 (-3, 22)
2 AND 3 AND 4	6 (23%)	23 (9, 35)	22	7 (-9, 25)

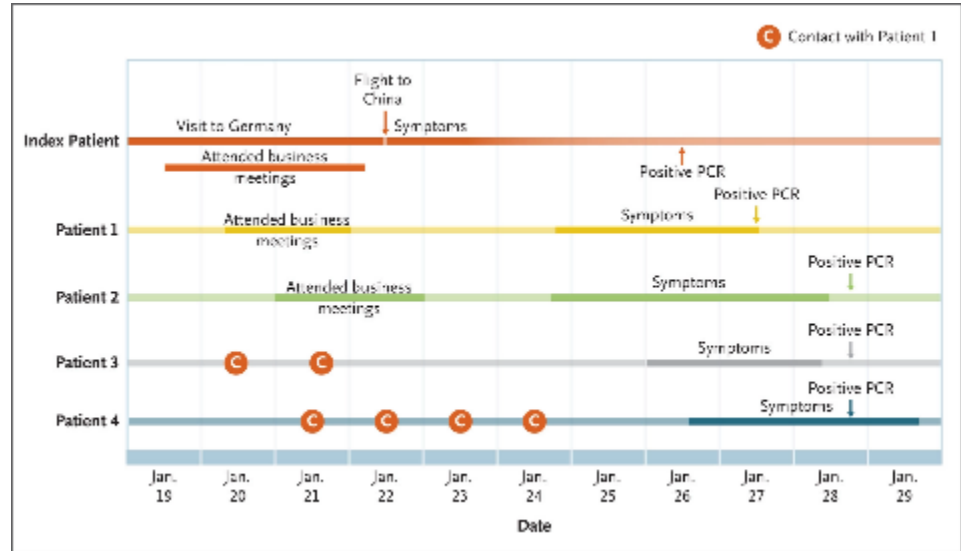
*95% confidence intervals estimated by bootstrapping with 1,000 resamples.

Entry screening was associated with an average of 7-12d delay in local transmission during 2009 A(H1N1) pandemic

Overview of state of the art and outline of key knowledge gaps – Knowledge gaps



“Notably, patient 1 or patient 3 who had visited Wuhan hospital might have been infectious before symptom onset because patient 5 was shedding virus without symptoms.”



Chan et al
Lancet 2020

Truly Asymptomatic Transmission ?

Rothe et al
NEJM 2020

Overview of state of the art and outline of key knowledge gaps – Knowledge gaps

Presumed Hospital-Related Transmission and Infection

Of the 138 patients, 57 (41.3%) were presumed to have been infected in hospital, including 17 patients (12.3%) who were already hospitalized for other reasons and 40 health care workers (29%). Of the hospitalized patients, 7 patients were from the surgical department, 5 were from internal medicine, and 5 were from the oncology department. Of the infected health care workers, 31 (77.5%) worked on general wards, 7 (17.5%) in the emergency department, and 2 (5%) in the ICU. One patient in the current study presented with abdominal symptoms and was admitted to the surgical department. **More than 10 health care workers in this department were presumed to have been infected by this patient.** Patient-to-patient transmission also was presumed to have occurred, and at least 4 hospitalized patients in the same ward were infected, and all presented with atypical abdominal symptoms. One of the 4 patients had fever and was diagnosed as having nCoV infection during hospitalization. Then, the patient was isolated. Subsequently, the other 3 patients in the same ward had fever, presented with abdominal symptoms, and were diagnosed as having nCoV infection.

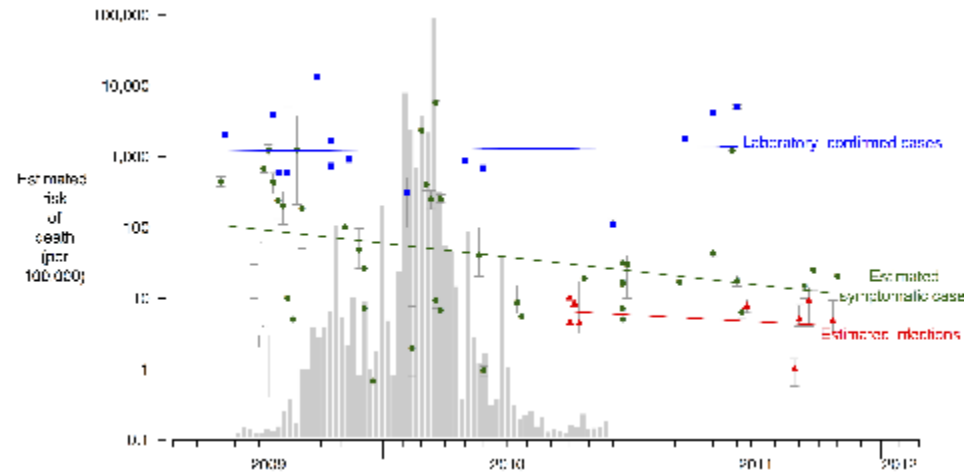
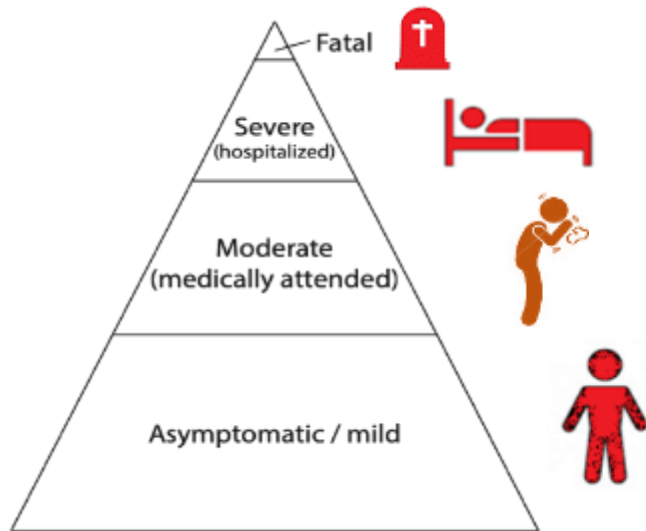
Wang et al *JAMA* 2020



Diamond Princess was carrying 2,666 passengers and 1,045 crew from a range of nationalities when it arrived at Yokohama on Feb 3. About half the passengers are from Japan. Local health authorities undertook screenings and ordered the quarantine after a man on the prior sailing was later diagnosed with 2019-nCoV in HK. As of Feb 10, 2020, 135 cases have been confirmed amongst those on board.

Overview of state of the art and outline of key knowledge gaps – Knowledge gaps

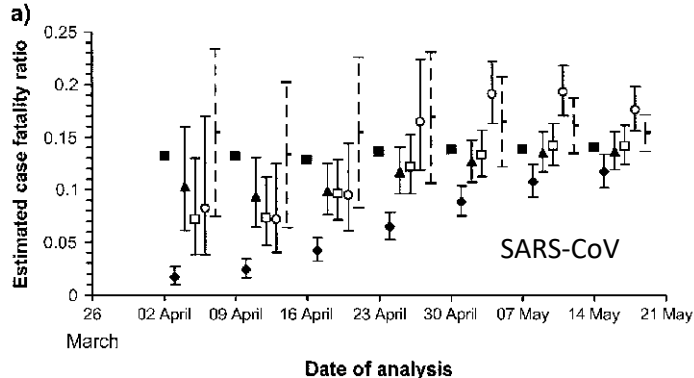
Figuring out the clinical iceberg



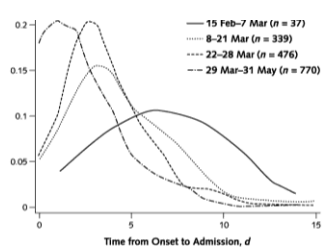
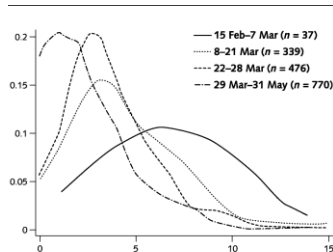
pH1N1 2009: problem with *numerator and denominator*

Numerator of “confirmed” deaths likely to underestimate impact on the elderly
Denominator of confirmed cases led to overestimation of CFR by several orders of magnitude

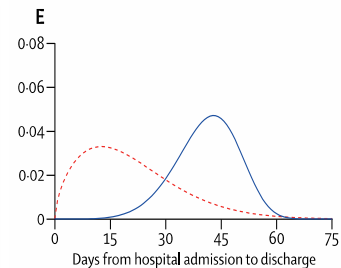
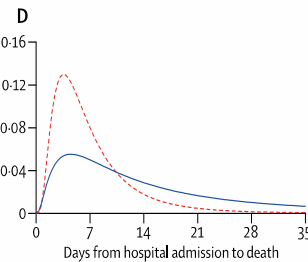
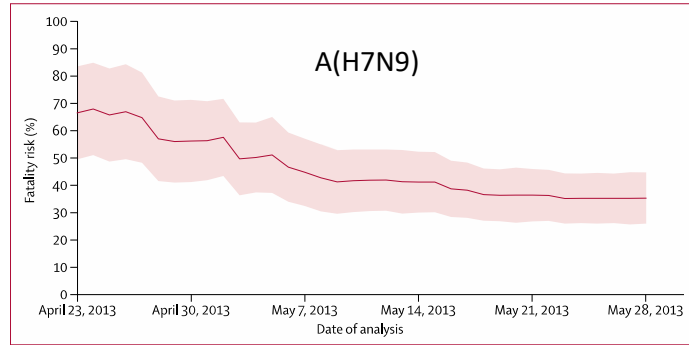
Overview of state of the art and outline of key knowledge gaps – Knowledge gaps



- Observed case fatality ratio
- ▲ Simple estimate 2
- Range from KM-like method
- ◆ Simple estimate 1
- KM-like method
- Gamma mixture model



Leung et al *Ann Intern Med* 2004
 Ghani et al *Am J Epidemiol* 2005

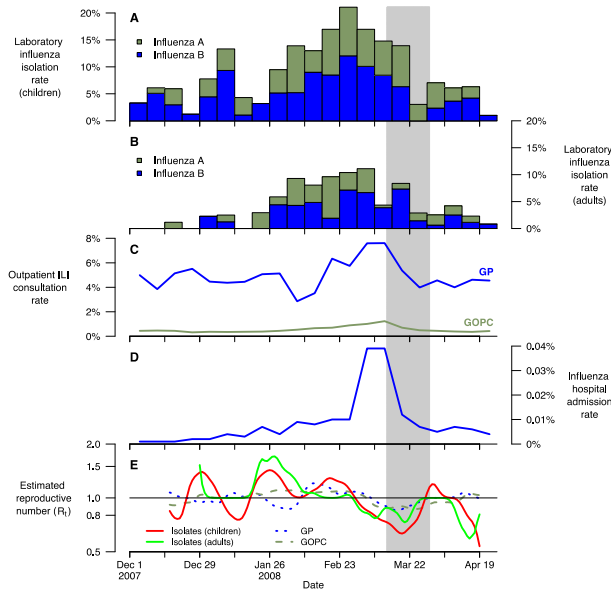


Yu et al *Lancet* 2013

Overview of state of the art and outline of key knowledge gaps – Knowledge gaps

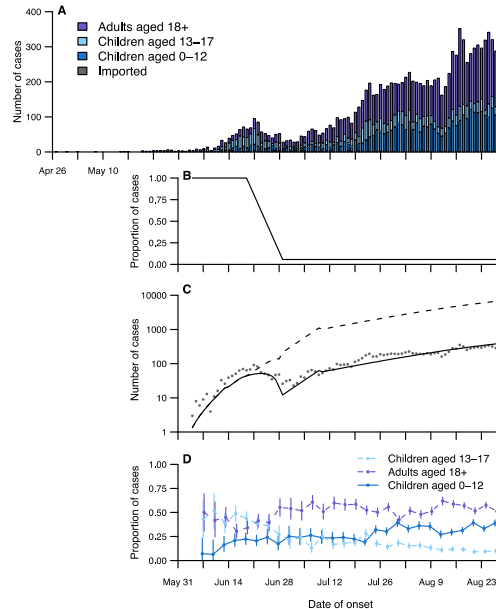
Should schools be/remain closed, and for how long? **Susceptibility**, **severity** and **infectivity** in children

2008...too little, too late



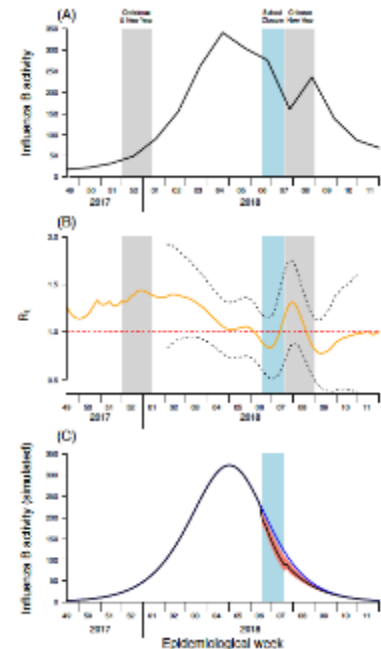
Cowling et al. 2008 *EID*

2009...12-25% reduction in transmissibility...peak delayed



Wu et al. 2010 *EID*

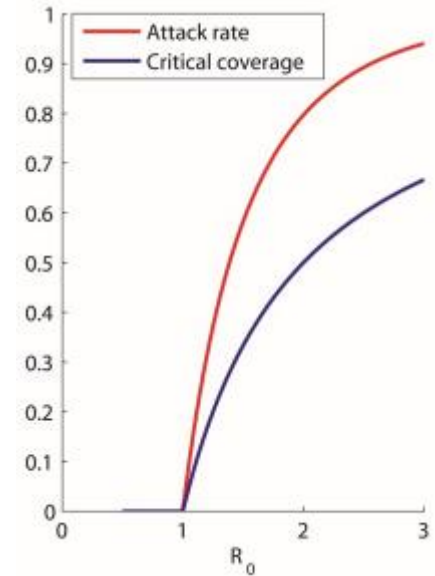
2018 Flu B



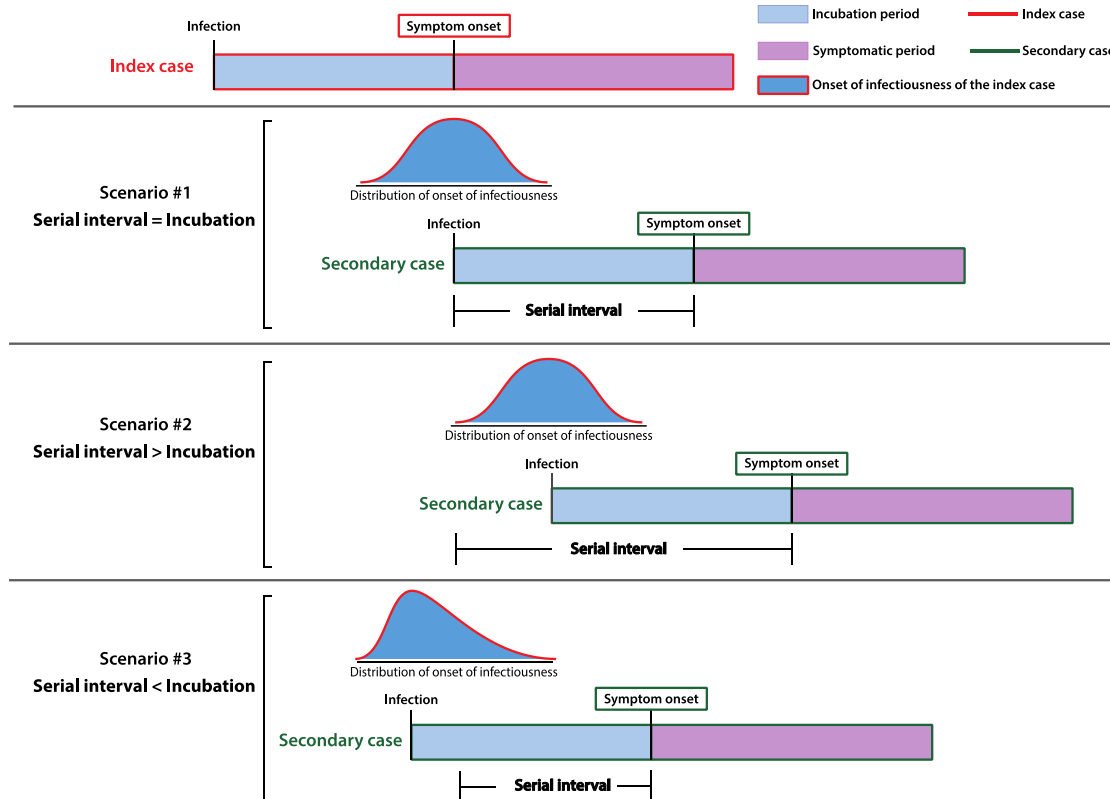
Ali et al. 2018 *EID*

Overview of state of the art and outline of key knowledge gaps – Knowledge gaps

Pathogen	R_0	Serial interval/ Generation time	Source	Methods
2019-nCoV	2.2 (1.4-3.9)	7.5 (5.3-19)	Li et al [1]	Serial interval was estimated from dates of symptoms onset of 6 infector-infectee pairs assuming SARS priors [2]; R_0 was estimated from the epidemic growth rate.
	2.68 (2.47-2.86)	8.4 (assumed)	Wu et al [3]	Serial interval was assumed to be the same as SARS; R_0 was estimated by fitting a transmission model to the estimated epidemic size of Wuhan based on the number of cases exported to cities outside mainland China, with assumptions of zoonotic force of infection.
	2.6 (1.5-3.5)	8.4 (assumed)	Imai et al [4]	Serial interval was assumed to be the same as SARS; R_0 was estimated by fitting a transmission model to the estimated epidemic size of Wuhan based on the number of cases exported to cities outside mainland China, with assumptions of zoonotic force of infection.
	3.11 (2.39-4.11)	5.61 (4.35-7.23)	Read et al [5]	R_0 and serial interval were jointly estimated by fitting a deterministic SEIR model to the daily number of confirmed cases in Wuhan and in major cities outside Wuhan in mainland China, and cases exported outside mainland China, assuming incubation period of 4 days.
	1.6-2.9 (R_t)	7.7 (assumed)	Kucharski et al [6]	R_t was estimated by fitting a stochastic transmission model to 1) daily incidence of cases exported outside mainland China, 2) daily incidence in early phase in Wuhan with no market exposure, and 3) daily incidence of initial cases in mainland China, assuming incubation period of 4.8 days and infectious period of 2.9 days.
	2.0-3.3 (R_t)	--	Majumder et al [7]	R_t was estimated by fitting the cumulative epidemic curve to Incidence Decay and Exponential Adjustment (IDEA) model.
SARS	2.2-3.6	8.4 (SD 3.8)	Lipsitch et al [2]	R_t was estimated from the rate of exponential growth in the number of cases in several other settings and with the use of data from Singapore on the mean serial interval.
	2.7 (2.2-3.7)	--	Riley et al [8]	R_0 was estimated by fitting a stochastic transmission model accounting for the effects of superspreading events.
	1.63 (Singapore) 1.88 (Beijing)	--	Lloyd-Smith et al [9]	R_0 was estimated from an integrated statistical analysis of the influence of individual variation in infectiousness on disease emergence.
MERS	0.47 (0.29-0.80)	--	Kucharski et al [10]	R_0 was estimated from branching processes with the offspring distribution following a negative binomial distribution.
	0.45 (0.33-0.58)	6.8 (6.0-7.8)	Cauchemez et al [11]	R is decomposed into mutually exclusive categories arising from within-cluster transmission, from within-region transmission and from between-region transmission.
	0.91 (0.36-1.44)	--	Chowell et al [12]	R_t was estimated from transmission trees reconstructed from successive cases with epidemiologic links.



Overview of state of the art and outline of key knowledge gaps – Ongoing research efforts



Overview of state of the art and outline of key knowledge gaps – Ongoing research efforts

Transmissibility

Analysis of clusters; household transmission studies; estimating transmission parameters from epidemiological data from different locations; viral shedding studies from exposure to recovery/death

Disease Severity

Case-control and cohort studies; population-wide surveillance; reports from clinical cohorts

Susceptibility

Household transmission studies; convalescent and population-based serological studies

Control and Mitigation Measures

Modeling analysis; comparisons of different locations and mitigation measures

Overview of state of the art and outline of key knowledge gaps – **Conclusions**

- Better estimates of key epidemiological parameters to infer transmissibility
- Robust estimates of disease severity is the most urgent question
- Comparative studies across multiple epicentres are needed to understand all aspects of transmissibility
- Serosurveys in stratified unselected samples in multiple epicentres are urgently required
- Determine if children are infected, and if so, if they are infectious

Overall goals of a global research roadmap: epidemiological studies

Objective 1: Understand transmissibility

Objective 2: Understand disease severity and susceptibility

Objective 3: Evaluate control and mitigation measures

Research priorities: Transmissibility

1. Provide robust estimates of the serial interval and generation time
2. Estimate effective reproductive number (R_t) in other cities (i.e. ex-Wuhan) in China and elsewhere
3. Clarify the relative importance of pre-symptomatic / asymptomatic transmission
4. Determine the role of different age groups in transmission, particularly children
5. Determine the relative importance of possible modes of transmission
6. Determine environmental effects on virus survival and transmission

Research priorities: Disease Severity & Susceptibility

1. Provide robust estimates of the risk of fatality of hospitalized cases, by age or other important groupings
2. Provide robust estimates of the risk of fatality of symptomatic cases, by age or other important groupings
3. Identify groups at high risk of severe infection
4. Determine if children are infected, and if so, if they are infectious
5. Determine if all infections result in neutralising immunity

Research priorities: Evaluate Control and Mitigation

1. **Provide impact estimates of travel restrictions, border screening and quarantine policies on non-local spread**
2. **Estimate the effects of social distancing measures and other non-pharmaceutical interventions on transmissibility**
3. **Predict the most effective measures to reduce the peak burden on healthcare providers and other societal functions**

Clinical characterization and management

- **State of the art**
- **Knowledge gaps**
- **Ongoing research efforts**

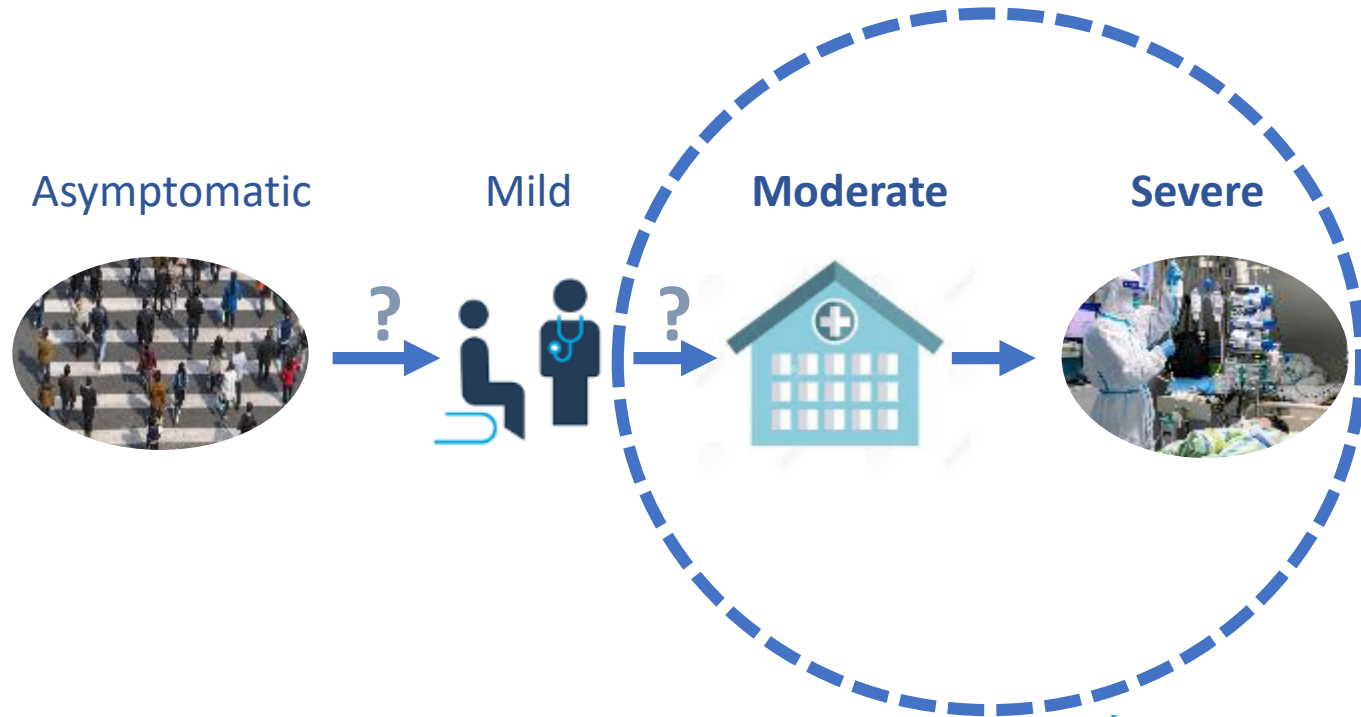
List of questions to be addressed

1. What is natural history of disease, prognostic factors for severe disease, including pregnant women and young children?
2. The relationships between viral load, location, antibody responses, and clinical disease and transmissibility? optimal sampling protocols for diagnosis?
3. What are the core endpoints for clinical trials.
4. What is optimized standard of care for the disease? adjuvant therapies for patients and contacts? supportive care interventions for critically ill patients?
5. How to operationalize implementation by capitalizing on clinical trial networks?

Clinical Characterization and Management: **Dedication to Patients**



Clinical Characterization and Management: Illness Spectrum



Overview of state of the art and outline of key knowledge gaps – State of the art

JAMA | **Original Investigation** | **CARING FOR THE CRITICALLY ILL PATIENT**

doi:10.1001/jama.2020.1585

Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China

Dawei Wang, MD; Bo Hu, MD; Chang Hu, MD; Fangfang Zhu, MD; Xing Liu, MD; Jing Zhang, MD; Binbin Wang, MD; Hui Xiang, MD; Zhenshun Cheng, MD; Yong Xiong, MD; Yan Zhao, MD; Yirong Li, MD; Xinghuan Wang, MD; Zhiyong Peng, MD

- **138 consecutive hospitalized patients**
 - Zhongnan Hospital, Jan 1 to Jan 28
- **Age 56 years** (IQR, 42-68; range, 22-92)
- **Sex:** 54.3% Men
- **Comorbidities:** 46.4%
 - Hypertension (31.2%)
 - Cardiovascular (14.5%)
 - Diabetes (10.1%)

Symptoms

Fever	98.6%
Fatigue	69.6%
Dry Cough	59.4%
Anorexia	39.9%
Myalgia	34.8%
Dyspnea	31.2%
Sputum	26.8%
Sore throat	17.4%

White cells	4.5 (3.3-6.2)
Lymphocytes	0.8 (0.6-1.1)
Neutrophils	3.0 (2.0-4.9)
Platelets	163 (123-191)
Creatine kinase	92 (56-130)
Lactate dehydrog	261 (182-403)
Bilirubin	9.8 (8.4-14.1)
Creatinine	72 (60-87)
Procalcitonin	49 (35.5%)



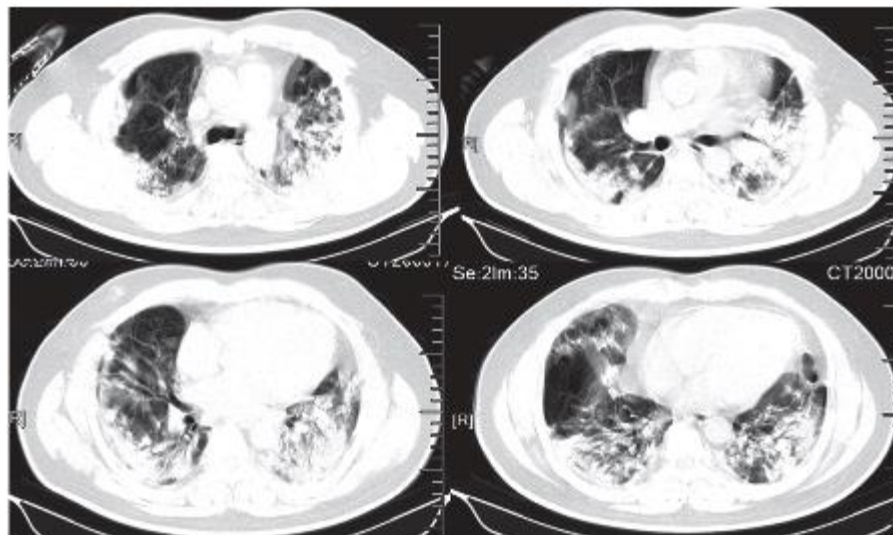
Overview of state of the art and outline of key knowledge gaps – State of the art

JAMA. doi:10.1001/jama.2020.1585

Onset of symptoms to:

Dyspnea	5.0 (1.0-10.0) days
Hospital Admit	7.0 (4.0 - 8.0) days
ARDS	8.0 (6.0-12.0) days

Incubation mean 5-6 (range 2-14) days*



Critically Ill Patients were

Older (66 years vs 51 years)

More likely to have **comorbidities** (72.2% vs 37.3%)

	No. (%)			P Value ^a
	Total (N = 138)	ICU (n = 36)	Non-ICU (n = 102)	
Complications				
Shock	12 (8.7)	11 (30.6)	1 (1.0)	<.001
Acute cardiac injury	10 (7.2)	8 (22.2)	2 (2.0)	<.001
Arrhythmia	23 (16.7)	16 (44.4)	7 (6.9)	<.001
ARDS	27 (19.6)	22 (61.1)	5 (4.9)	<.001
AKI	5 (3.6)	3 (8.3)	2 (2.0)	.11
Treatment				
Antiviral therapy	124 (89.9)	34 (94.4)	90 (88.2)	.36
Glucocorticoid therapy	62 (44.9)	26 (72.2)	36 (35.3)	<.001
CRRT	2 (1.45)	2 (5.56)	0	>.99
Oxygen inhalation	106 (76.81)	4 (11.11)	102 (100)	<.001
NIV	15 (10.9)	15 (41.7)	0	<.001
IMV	17 (12.32)	17 (47.22)	0	<.001
ECMO	4 (2.9)	4 (11.1)	0	.004

Overview of state of the art and outline of key knowledge gaps – State of the art

Of 138 **HOSPITALIZED** Patients*

85 patients (61.6%) **still hospitalized**

47 patients (34.1%) **discharged**

6 patients (4.3%) **died**

Median stay 10 (7.0-14.0) days

Of 36 **ICU** patients*

11 (31%) still in the **ICU**

9 (25%) discharged **home**

10 (28%) transferred to general **wards**

6 (17%) **died**

Mortality of hospitalized patients is still uncertain but *may* be >5-15%*, **

Overview of state of the art and outline of key knowledge gaps – State of the art (*IPC)

- **Nosocomial transmission 41% patients (N=57)**

- ❖ **Patients other admit diagnoses (12.3%, N= 17)**

- ❖ **Health professionals (29%, N=40) ***

- 31 (77.5%) on general wards
- 7 (17.5%) in the emergency department
- 2 (5%) in the ICU

* 10 Health professionals presumed infected by one patient

Overview of state of the art and outline of key knowledge gaps – Knowledge gaps

- Natural history and clinical course particularly in special populations:
 - **severely ill, pregnant, children, elderly**
- Optimal selection of **anti-viral agents** and interventions targeting the virus convalescent plasma, poly- and monoclonal antibodies, IVIg (*therapeutics)
 - **Compassionate use** in the absence of controlled trials is now ongoing.
- Optimal selection of strategies for adjunctive therapies
 - **immunomodulatory agents (IL-1ra, interferon), steroids, ACE inhibitors, vitamin C, statins, anti-arrhythmics**

Overview of state of the art and outline of key knowledge gaps – Knowledge gaps

- Optimal selection of supportive care (ICU) interventions,
 - **oxygen or fluid management strategies**
 - **ventilation strategies**
- Reducing nosocomial spread. (*IPC/lab/social science)
 - **mode of nosocomial spread: direct patient care or other non-patient areas, ventilation**
- Viral kinetics to inform clinical care and discharge criteria (*Lab/IPC)
 - **shedding of virus, transmissibility**
 - **optimal sampling techniques**

Overview of state of the art and outline of key knowledge gaps – Ongoing research efforts

85 registered studies in China

- 34 recruiting interventional studies (including lopinavir/ritonavir, remdisivir) washed microbiota transplantation, arbidol, glucocorticoids, steroids, ruxolitinib combined with mesenchymal stem cell infusion, TCM, hydroxychloroquine, nasal high-flow preoxygenation assisted fibre-optic bronchoscope intubation.
- 51 non-recruiting studies interventional studies (favipiravir, baloxivir, arbidol, interferon, darunavir/cobicistat), interferon, intravenous Immunoglobulin, hydroxychloroquine steroids, umbilical cord blood mononuclear cells and traditional Chinese medicines.
- Mental health and psychological interventions on doctors, nurses and patients*

Overview of state of the art and outline of key knowledge gaps – Conclusions

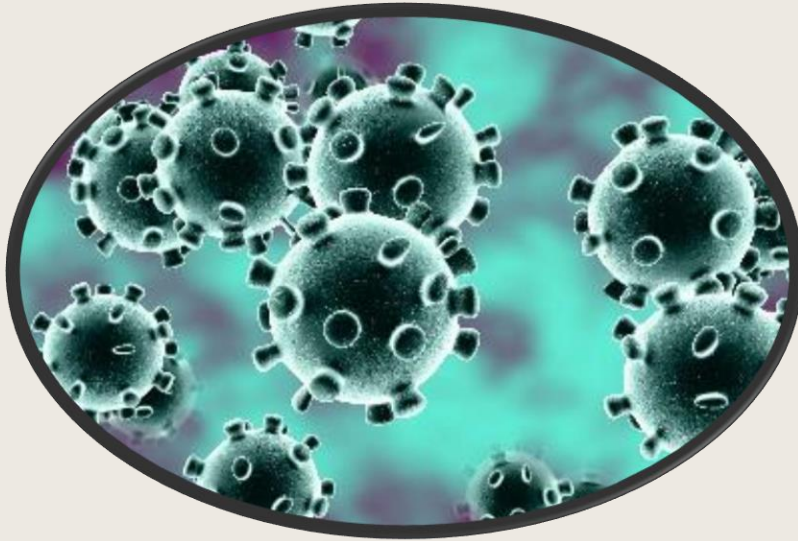
- Recent observational studies are providing some initial clinical characterization, but questions remain.
 - Special populations such as young children and pregnant women,
 - Outcomes in hospitalized patients,
 - Viral kinetics, transmission
 - Effective antiviral, adjunctive and supportive care therapies.
- Ongoing clinical studies and trials are addressing some of these issues, but mapping of studies/trials needs to be rapidly done
 - Core CRF and core outcomes are essential.
 - Implementation of clinical trials using clinical networks

2019 novel Coronavirus
Global research and innovation
forum: *towards a research roadmap*



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to prevent epidemics



**Infection prevention and
Control, including protection
of health care workers**

John Conly, Canada

Anna Levin, Brazil

Infection Prevention and Control including Protection of Health Care Workers

Overview

- State of the art
- Knowledge gaps
- Ongoing research efforts



Nature NEWS
07 February 2020

Did pangolins spread coronavirus to people?

State of the art – 2019n-Cov detection

Patient specimens

- **BAL samples** (Zhu NEJM 2020) + viral isolation
- **Nasopharyngeal/oropharyngeal (NP/OP) swabs**
 - multiple reports of detection in NP/OP swabs; sensitivity and specificity not known
 - shedding over time - Chan (Lancet 2020) found + RT-PCR in NP/OP swabs of a child with CT changes c/w infection but reportedly ‘asymptomatic’
 - exact **duration of shedding not known** with certainty
- **Serum**
 - Chan (Lancet 2020) also showed + RT-PCR of serum in one patient
- **Stool**
 - Investigators in Shenzhen and Washington State have detected 2019-nCoV **RNA in the stool of infected patients** (ProMed, Holshue NEJM 2020)
 - No reports have demonstrated live virus recovery in stool for 2019-nCoV

State of the art – 2019-nCov

Environmental specimens

- Potential **intermediate host (pangolin)** based on 99% WGS similarity (Nature News Feb 7 2020)

Healthcare workers (HCWs)

- Looking at three separate time intervals (before Jan 1, Jan 1-11, Jan 12-22), **0%, 3%, and 7% HCW infections** reported in a series of 425 Chinese patients from Wuhan (Li, NEJM)
- **One HCW** reported as a confirmed case **outside of China**
- In a single-center case series of 138 hospitalized 2019-nCoV confirmed cases in Wuhan, China, presumed **hospital-related transmission** was suspected in 41% of patients (Wang, JAMA)

Public health interventions - mathematical modeling

- Reproductive number **range $R_0 = 1.96$ to 6.47** (Du et al, Medrxiv; Tang et al, Clin Med)
- Effectiveness of intervention measures; enhancing quarantine/isolation (including travel restriction) following contact tracing and reducing contact rate can significantly lower the peak and reduce the cumulative predicted number of infected individuals (Tang, Clin Med)

State of the art – 2019-nCov – ongoing research

84 ongoing research studies on 2019n-Cov (WHO-International Clinical Trials Registry Platform): NONE are on IPC but may be non-registered

Source: <http://apps.who.int/trialsearch/AdvSearch.aspx?SearchTermStat=117&ReturnUrl=%7e%2fListBy.aspx%3fTypeListing%3d0>

Current research

- SR on use of **masks in the community**
- **Feasibility of environmental sampling /screening** of people under **quarantine**
- Epi study of **2⁰ and 3⁰ generation transmission**
- **Environmental sampling of surfaces** surrounding the **affected patients**
- PCR tests on respiratory secretions of affected patients **by day of illness**

State of the art - evidence from SARS-CoV and MERS-CoV relevant to IPC

- **Droplet and contact** – multiple studies demonstrated **compliance with gloves, gowns and medical masks or N95s** were adequate to prevent transmission for SARS; **major risks** exposure of eye and mucous membranes to **resp secretions and AGMPs**, ie intubation (**opportunistic airborne**); no association with contact with urine/stool
- **HCW spread** - associated with **inconsistent or improper PPE use** for SARS/MERS-CoV outbreaks; **Infections in HCWs: 22% and 25%** for SARS and MERS, respectively
- **Risk factors for nosocomial spread** of MERS-CoV in two large outbreaks in Saudi Arabia and South Korea found ER/Ward **overcrowding and sub-optimal control of visitors** were factors
- **Transmission** of MERS-CoV **was not documented** in an investigation of mostly **asymptomatic** and **pauci-symptomatic** cases and their household contacts
- **Asymptomatic cases uncommon** – one study of MERS cases found 80% of “asymptomatic” persons actually had symptoms on close questioning

IPC research gaps and respective priorities (1)

1. Modes of transmission

- Body fluids, target tissues for entry, **airborne spread, vertical transmission**

2. Duration of transmission

- **Duration of shedding, asymptomatic shedding**, duration IPC precautions

3. Environmental stability

- **Viral survival** on surfaces and other media, factors influencing stability

4. PPE and IPC measures

- Relative **importance of specific PPE/IPC** measures, type of mask and eye protection, airborne vs droplet precautions, PPEs for triage, spatial separation distances, **risks factors for HCWs' exposure**

IPC research gaps and respective priorities (2)

5. Cleaning, disinfection, and waste management

- Efficacious **disinfectants**, treatment of sewage, UVGI, surface coating

6. Isolation and quarantine

- **Cohorting vs single rooms**, costs and resource implications for cohorting, criteria for, principles and cost-effectiveness of quarantine, and unintended consequences of quarantine and isolation

7. Behavioural change and social science

- Best approaches to **communicate policy recommendations**, role of media coverage, precautions for home care, most frequent IPC lapses, barriers and facilitators influencing HCWs compliance, human factors & ergonomics, isolation and PPE fatigue

8. Community IPC

- **Use of mask by healthy people, precautions for home care**, community/family members education, dead bodies

9. Innovation

- **Point of care (PoC) testing, PoC sensors and wearable monitoring**, technologies to avoid unnecessary exposure and transmission, engineering, chemistry and molecular science of surfaces, design to minimise touchpoints in acute health care facilities

Ensuring coordination across research areas

- Virus - natural history, transmission and diagnostics
- Animal and environmental research (to inform outbreak control measures)
- Epidemiological studies
- Clinical characterization and management (IPC in specific procedures)
- Therapeutics R&D (prophylaxis)
- Candidate vaccine R&D (prevention in community and HCWs)
- Ethical considerations for research
- Integrating social sciences in the outbreak response (behavioural change)

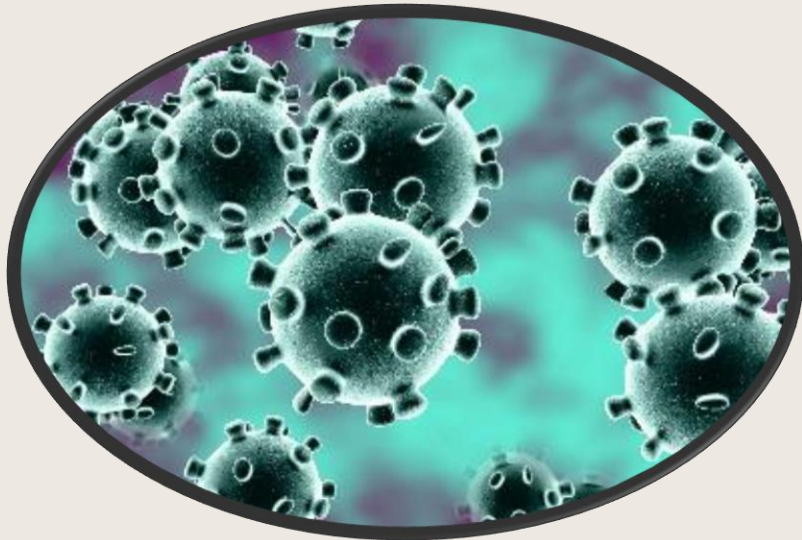
Conclusions

- Many **core principles** already **exist for IPC** based on previous documents
- Need to **ensure co-ordination across other themes** to allow science to direct IPC recommendations if 2019-nCov differs substantially from other known zoonotic CoVs
- **IPC recommendations** should be **evidence-based**
- Need to engage investigators globally to expediently conduct **high quality studies** to enhance the ipc evidence base

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Thematic area: Therapeutics

Dr Marco Cavaleri



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Overview of state of the art and outline of key knowledge gaps – State of the art

- A landscape of therapeutics was drawn to summarize the existing evidence to support their use against 2019-nCoV
- Prioritization exercise:
 - Remdesivir
 - Lopinavir/Ritonavir + (interferon- β)
- Master Protocol being developed for a multi-center adaptive RCT to evaluate the efficacy and safety of investigational compounds
- In vitro and modelling studies
- Ongoing clinical trials in China: e.g. Randomized, Double-blind, placebo-controlled studies to evaluate the efficacy and safety of Remdesivir (mild/moderate and severe cases)

Overview of state of the art and outline of key knowledge gaps – Knowledge gaps

- Insufficient knowledge of clinical evolution of 2019-nCoV disease
- Insufficient epidemiological information to precisely guide the definition of the target population and end-points for efficacy trials
- In vitro/in vivo activity against 2019-nCoV
- The appropriate dosage of therapeutics to use against 2019-nCoV
- Data on efficacy and safety of available candidate therapeutics against 2019-nCoV

Overview of state of the art and outline of key knowledge gaps – Ongoing research efforts

- In vitro studies of antiviral agents
- Cross-reactivity studies to evaluate mAbs developed against SARS
- Clinical trials in China (>85):
 - Remdesivir
 - Lopinavir+Ritonavir
 - Tenofovir, Oseltamivir, Baloxivir marboxil, Umifenovir
 - Novaferon
 - IFNs
 - Chloroquine
 - Traditional Chinese Medicines: Lianhua Qingwen

Overview of state of the art and outline of key knowledge gaps – **Conclusions**

- No therapeutics have yet been licensed against 2019-nCoV
- In order to reduce mortality and improve clinical disease outcome there is an urgent need to prioritize investigational candidates most suitable for efficacy trials
- Clinical trials conducted under a Master Protocol will aim to evaluate the efficacy and safety of these therapeutics across multiple locations

List of questions to be addressed

1. In addition to the current prioritized therapeutics (remdesivir, liponavir/ritonavir), what other Rx could be considered (e.g. other repurposed drugs, mAbs, polyclonal Abs, convalescent plasma, new compounds)
2. Role of IFNs - Role of host-targeted therapies
3. Pre-clinical studies: in vitro/animal models
4. Efficacy trials protocols (end-points and selected trial population)
5. Post-exposure prophylaxis and/or prophylaxis studies

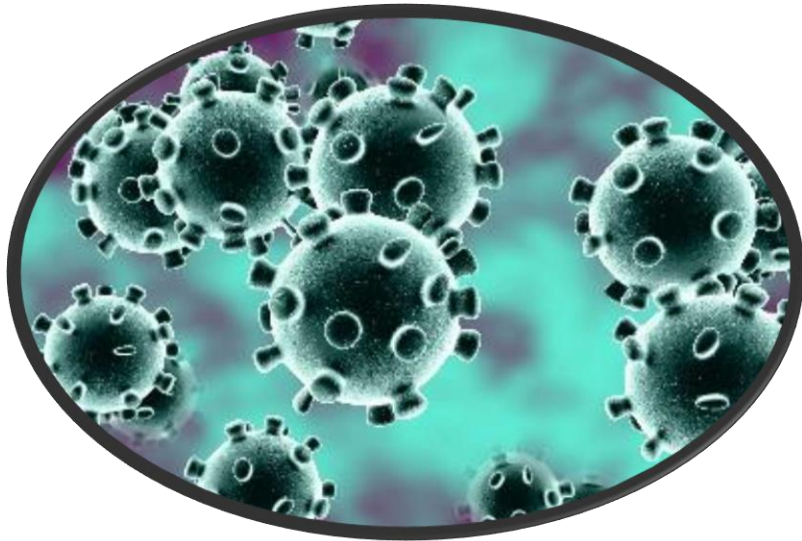
Overall goals of a global research roadmap?

Objective 1: Identification of candidates for clinical evaluation in addition to the ones already prioritized

Objective 2: Multicenter master protocol to evaluate efficacy and safety

Objective 3: Coordinated collaboration for therapeutics evaluation

2019 novel Coronavirus Global research and innovation forum: *towards a research roadmap*

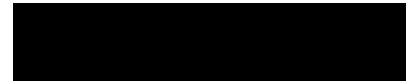


Candidate Vaccines R&D Subgroup



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Overview of state of the art and outline of key knowledge gaps

- **State of the art**
- **Knowledge gaps**
- **Ongoing research efforts**

Objectives

1. Develop a research plan that will facilitate the development and evaluation of nCoV vaccines.
2. Provide a mechanism to promote performance of key research tasks, and to share information about performance.

Disclaimer: This presentation includes incomplete discussions that are the result of brainstorming sessions. The group hasn't yet reached clear conclusions about these issues.

Overview of state of the art and outline of key knowledge gaps – State of the art

Activity	Complete?
List of candidate vaccines developed against nCoV	✓
List of candidate vaccines developed against SARS	✓
List of candidate vaccines developed against MERS	✓
List of coronavirus animal model	✓
Preliminary vaccine prioritization for clinical trials (nCoV)	✓
Summary of evidence on vaccination-related disease enhancement	Ongoing
Assessment of cross-reactivity of nCoV with other coronaviruses	Ongoing
Vaccine Efficacy Trial Master protocol synopsis	✓
Vaccine Efficacy Trial Master protocol	Ongoing
Mapping of viruses and reagents	✓
nCoV structural characterization	✓

Overview of state of the art and outline of key knowledge gaps – State of the art

	# of candidates vaccines	Pre-Clinical Stage	Clinical Stage
nCoV	5	5	0
SARS-CoV*	33	31	2
MERS-CoV*	48	45	3

*Studies to assess immunological cross-reactivity with other coronaviruses being planned

	MERS	SARS
# of animal models	8	7

Animal models

- Mouse is obvious first choice. Additional models should be studied to see which models best mimic human infection and may be best suited to studying enhanced disease or identifying potential correlates of protection. Animal models are also useful in evaluation of antivirals.
- Discussion of animal models needed for 1st-in-human studies. Prioritization and other needs may be different from regulatory needs. Animal models may help to address preclinical enhancement issues, but other strategies may also be employed (e.g., informed consent, initial vaccination of volunteers at low risk for nCoV exposure)
- CEPI is supporting work on ferret model in Australia.

Immune response assays

- ELISA
 - For vaccine response as well as evaluation of background seropositivity
 - Standards may be important
- Neutralization
 - BSL-3
 - BSL-2 (pseudovirions)
 - Will need comparison/validation of results relative to nCoV neutralization (note that pseudovirion neutralization for MERS was more sensitive than PRNT, though with correlation)
 - Strategies include lentivirus, VSV, different nCoV components
 - Large stocks for distribution will be useful
- Analysis of CD4+, CD8+, and cytokine responses to determine which if any are related to protection or enhancement of disease.

Evaluating potential for enhanced disease

- Potential importance of cellular tropism (monocytes/macrophages)
- Potential importance of CD8-mediated immune responses
- Potential importance of high neutralizing responses
- Animal models to study enhanced disease
- Role of human clinical trials to evaluate enhanced disease

Clinical trial/Study design

- Study design
 - Phase I, II
 - Goals: safety, comparison and prioritization of vaccine candidates
 - Phase III
 - Goals: Demonstrate safety, efficacy and evaluate potential for enhancement of disease
 - Phase IV
 - Goals: Additional real-world safety and effectiveness
- Should vaccine be tested in those with greatest risk from disease (e.g., elderly, immunocompromised) vs. those in whom clinical trials could most expeditiously evaluate efficacy? Immunogenicity in these special target groups will nonetheless be important to evaluate.
- Importance of clinical endpoint efficacy studies

Cell culture

- Required to optimize neutralizing assays, grow up virus stocks for other experiments including evaluation of cross-reactivity. Virus reported to grow well in Vero cells.
- Important to know that virus will stay genetically stable through cell culture passage. Sequencing results pending from several labs.
- Large stocks will be useful, including standardized stocks for challenge experiments.
- Also important for antivirals

Cross-reactivity

- Antigens
- Monoclonals vs. SARS, MERS
- Antibodies vs. nCoV
- Other

Working Group on Vaccine Prioritization

“Participants recommended that, given current knowledge and vaccine development status, vaccine approaches targeting the novel coronavirus should be prioritized for further development over vaccine approaches targeting other coronaviruses in the context of the nCoV global outbreak, noting that the development of vaccines for other coronaviruses remains a public health priority.”

For individual vaccine candidates

- Potency assays for individual vaccines
- Process development (may be more complex for live-attenuated or vectored vaccines)
 - Formulation (excipients, adjuvants and preservatives)
 - Filtration (for sterility)
 - Storage temperature (stability)
 - Route of administration
 - Presentation (monodose vs. multidose; lyo vs liquid)
 - Process validation
 - Consistency

Note this is a partial list, and is not intended to be comprehensive at this stage

Relating TPP to vaccine candidate prioritization

- A. 1 dose
- B. Potential for high level neutralizing Ab
- C. previously proven strategy
- D. likely to induce cytotoxic CMI response
- E. Lower theoretical risk of enhancement?
- F. Speed of development,
- G. Capability to rapidly make large quantities of vaccine
- H. Duration of immunity
- I. Vaccine stability (i.e. not prone to mutation)
- J. Cost/dose

Vaccine type

- Inactivated/adjuvanted
- Subunit/adjuvanted
- Live-attenuated
- Vectored
- DNA
- RNA

Potential Advantages#

- B,C,F
- B,C*
- A,B,C,D,E
- A*,B,C*,D,E,G
- B,D,E,F,G
- B,D,E,F

*May be an advantage for some examples of this vaccine type

#This is notional and not meant to portray conclusions about advantages or disadvantages of any specific vaccine

Overlap areas

- Natural history of disease
 - Pathogenesis in humans, cause of death, etc.
 - Kinetics and durability of virus-specific humoral and cellular immune responses in mild-moderate and severe (survivors and non-survivors) of nCoV illness
 - Extent of subclinical infection
 - Shedding sites (early results suggest significant shedding)
 - Clinical data to support case definition for clinical trial endpoints (fever+viremia vs. severe disease, perhaps other endpoints should be considered if viremia is transient?)
- Epidemiology
 - Attack rates/fatality rates/modeling?
 - Will support clinical trial design
- Diagnostics
 - Assays to support case definition for clinical trials and epidemiological studies
 - PCR assays
 - Other case-definition related assays

Web-based Data Sharing Tool

- Who has reagents? (Currently, more detail is available in summary of most recent Cross-reactivity workgroup call)
 - Virus (in China, Australia, UK, Canada, France, Germany, US, others)
 - Purified spike protein (VRC) and spike protein subunits and domains (WRAIR) (in limited supply)
 - Plasmid used to express spike protein (VRC) and spike protein subunits and domains (WRAIR)
 - Serum and B cells (in very limited quantities, request through US government)
 - Monoclonals (production underway)
- Who is working on key questions?
- What are results?
- What are needs?

Key research reagents for vaccine development

- Standardized stocks
 - Viruses
 - Pseudovirions
- Standards for immunological assays

Other considerations

- Regulatory harmonization (esp. preclinical studies, clinical trial endpoints)
 - Will be topic of March 2020 meeting in Brussels, sponsored by ICMRA
- Manufacturing/filling capacity (in facilities that have been or could be inspected)
- Other manufacturing/testing considerations (e.g., containment)
- Access to clinical trial sites, etc.
- Intellectual property
- Are there other ways to facilitate sharing of reagents?
- Note parallel efforts (e.g., NIAID DMID/BARDA group to assign sub-groups to address some of these issues analogous to FANG for Ebola; NIBS working on challenge stocks, dose, route, etc.)

Overview of state of the art and outline of key knowledge gaps – State of the art (1/3)

Useful and authoritative ethical guidance documents are in place

- Substantial literature has emerged from past outbreaks
- Ethical issues have been well-characterized and researched, particularly in the domain of research ethics
- Infectious disease emergencies do not overrule need to uphold universal standards
- Accepted ethical principles admit to adaptation to circumstances

Ebola outbreak response shows that complex research undertakings can be successful (Saxena et al., 2019; London et al., 2018; Aarons et al., 2018; Schopper et al. 2017)

- Ethics review was not responsible for bottlenecks and delays in implementation in studies

Overview of state of the art and outline of key knowledge gaps – State of the art (2/3)

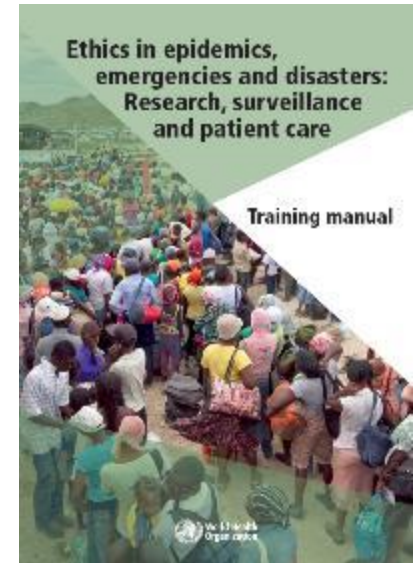
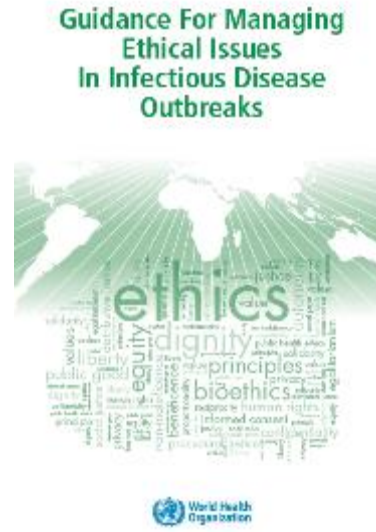
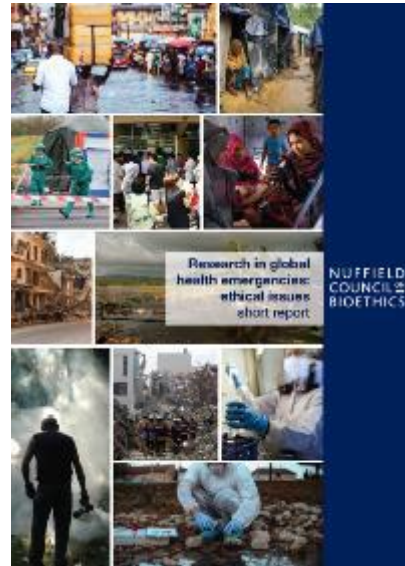
Ethical principles for multinational research exist (Emanuel et al., 2004)

- Collaborative Partnerships
- Social Value
- Scientific Validity
- Fair Selection of Study Population
- Favourable Risk-Benefit Ratio
- Independent Ethical Review
- Informed Consent
- Respect for Recruited Participants and Study Communities

Key ethical issues can be anticipated (Nuffield Council on Bioethics, 2020; Smith & Upshur, 2019)

- Community engagement
- Data sharing/data transparency
- Setting priorities of scarce resources
- Health care worker responsibilities and supports

Overview of state of the art and outline of key knowledge gaps – State of the art (3/3)



Overview of state of the art and outline of key knowledge gaps – Knowledge gaps

- **Ethics integration and knowledge translation strategy**
- **Harmonization of multiple reviews**
- **Biological Samples, biobanks, and consent**
- **Inclusion of pregnant women and children in clinical trials**
- **Companion social science studies**

Overview of state of the art and outline of key knowledge gaps – Ongoing research efforts

- **Ethics of public health countermeasures**
- **Adaptive trial designs**
- **Global governance**

Research Priority Questions

- 1. How are ethical considerations best integrated across the spectrum of research initiatives?**
- 2. What is the status of research ethics capacity globally for rapid implementation of therapeutic and vaccine trials?**
- 3. What substantive and procedural values should guide governance of the research initiative?**

Overview of state of the art and outline of key knowledge gaps – **Conclusions**

- Robust and sufficient ethics knowledge and guidance documents are already in place
- Ethics and ethics oversight are not barriers to research and innovation
- Key ethical issues in research can be anticipated: community engagement, data sharing and transparency, priority setting, health care worker supports
- Ethics contributions are, and should be, cross-cutting

Toward a functional governance framework

- Ethical considerations are crucial to governance (Eccleston-Turner et al., 2019)
- Adapt an ethical framework with substantive and procedural components
- Focus on transparency, accountability, adaptability, and inclusion
- Bear in mind the overarching importance of fostering and maintaining trust

Overview of state of the art and outline of key knowledge gaps

- **State of the art**
- **Knowledge gaps**
- **Ongoing research efforts**

1. What are effective strategies to promote acceptance and adherence to public health measures aimed at limiting 2019-nCoV human-to-human transmission?
2. How can we rapidly identify secondary impacts of the outbreak and outbreak control measures, and deliver effective strategies to mitigate potential harms?
3. What are effective strategies to ensure continuity and prevent overwhelm of clinical services (including sexual and reproductive health services)?
4. What is the best way to protect the physical and mental health of healthcare workers?
5. How can we rapidly involve communities in the design, delivery and dissemination of clinical research?
6. What are the best strategies to disrupt the flows of misinformation on social media platforms?

Overview of state of the art and outline of key knowledge gaps – **State of the art**

Impact of public health measures

Impacts of quarantine (Rubin et al 2020), to restrict travel, close schools, close businesses;
Secondary impacts: Lack of sufficient protective equipment (Mahase 2020), other healthcare needs (Woods 2020)

Social drivers of transmission

Growth in high speed train travel and air travel, Lunar New Year (Zhao et al 2020)

Impact on healthcare workers

Frontline staff, especially nurses, at risk; protective psychological factors – good IPC training, confidence in IPC, self efficacy in role, notions of solidarity, altruism, organizational support; Burnout/ PTSD risk factors: social isolation, risk of stigma, higher perception of risk of illness, inadequate training (Brooks et al 2018)

High circulation of myths and misinformation

Panic and mental health impact (Bao et al 2020); Social networks can be instrumental for spreading offline behaviours (Jones et al 2017)

Anticipate need for involvement and engagement in clinical research

Overview of state of the art and outline of key knowledge gaps – Knowledge gaps

Public Health

What are effective strategies to promote acceptance and adherence to public health measures aimed at limiting 2019-nCoV human-to-human transmission?; How can we rapidly identify secondary impacts of the outbreak and outbreak control measures, and deliver effective strategies to mitigate potential harms?

Clinical

What are effective strategies to prevent overwhelm of clinical services (incl. SRH services)?; How to protect the physical and mental health of healthcare workers?; How to involve communities in plans for clinical research?

Community engagement;

What are effective ways to engage large, urban populations?; What is the most effective way to systematically assess and address stigma and xenophobia related to 2019-nCoV?

Media and communication

How are people using social media?; What are best strategies to disrupt the flows of misinformation on social media platforms?; What are the best strategies to address stigma and xenophobia and promote acceptance and inclusion?

Sexual and reproductive health

How can we best communicate the risk of mother to child transmission for 2019-nCoV?

Overview of state of the art and outline of key knowledge gaps – Ongoing research efforts

Evaluating impact of public health measures:

Effectiveness of lockdown (lead: Xian Jiaotong University), Economic impact of extended business closures (lead: Zhejiang University), psychological and behavioural responses pre-post exposure to live animals (lead: Fudan University), implementation and performance of epidemic prevention strategies (lead: Shanghai Municipal People's Government Development Research Center) individual prevention behaviours (Pengpai), evaluating eGovernment as an info source (lead: Center for Public Policy Research at the East China Normal University and Research Institute)

Investigating role of early warning and emergency risk communication (China)

Evidence on protection of healthcare workers

Help seeking behaviours to manage patient demand

Stakeholder readiness to participate in medical research

Media surveillance

Public reaction (lead: Fudan Uni) For improved risk communications (lead: SoNAR-Global)

Overview of state of the art and outline of key knowledge gaps – **Conclusions**

Broad agenda flexible

Priorities shaped by needs and context at local, national and regional levels; must stay open to new agenda items

Operational endpoints

To be useful, research needs rigorous, rapid methods and quick turn around to inform operations; medium term academic track also important.

Social science contribution is cross cutting

Many priorities are cross cutting, needs for engagement with many different stakeholders to understand priorities and end user needs.

Overall goals of a global roadmap: social science research for operational response

Objective 1: To establish a framework for identifying priority areas where social science research can contribute to achieving the goals of the strategic response plan.

Objective 2: To build and strengthen networks of social science researchers operating in different global regions.

Objective 3: To support operational partners, with focus on local partners and national public health, with tools and evidence, to account for social and behavioural dynamics in their actions.

Research priorities: public health

1. What are effective strategies to promote acceptance and adherence to public health measures aimed at limiting 2019-nCoV human-to-human transmission, e.g. isolation, social distancing, quarantine, public health prevention advice etc.?
1. What are effective strategies to promote acceptance and adherence to infection, prevention and control measures in community settings?
1. How can rapid investigation of social drivers of transmission contribute most effectively to public health response measures?
1. How can we rapidly identify secondary impacts of the outbreak and outbreak control measures, and deliver effective strategies to mitigate potential harms?

Research priorities: clinical

1. What are effective strategies to ensure continuity and prevent overwhelm of clinical services (including sexual and reproductive health services)?
1. How can organisations best support the physical and psychological health of their staff, including clinical (nurse, doctors, allied health professionals, administration (managers, receptionists etc.) and support staff (cleaners, porters etc.)?
1. What are effective strategies to promote acceptance and adherence to infection, prevention and control measures among healthcare worker?
2. How can understanding of protective psychological factors from SARS contribute to strategies for mitigating burnout of healthcare workers?
1. How can understanding of patient and public help seeking behaviours through traditional and non-traditional routes inform strategies for self-triage and home care?
1. What are the best strategies for rapid engagement and good participatory practice for medical research?

Research priorities: media and communication

1. How are people using social media to access information? What drives deliberate circulation of conspiracy misinformation, stigmatizing and xenophobic messaging, and conspiracy regarding 2019-nCoV?
1. What methodologies exist for tracking and disrupting knowledge circulation (media, social media etc.)? Do we have the right levers to tackle the spread of misinformation?
1. How can insights around rumor spread help target communication and messaging for this outbreak?

Research priorities: engagement

1. What are effective methods to engaging priority community groups, including large urbanised populations, those working in travel and tourism, migrants, underserved populations?
1. What is the most effective way to systematically assess and address stigma and xenophobia related to 2019-nCoV?

Research priorities: sexual and reproductive health

1. What is the risk of mother to child transmission and sexual transmission of the 2019-CoV and how can we best communicate that risk?
1. What is the most effective way to ensure readiness to respond and expand on social science needs in SRH according to new evidence generated?