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Sent: Thur 5/28/2020 1:24:01 PM
Subject: protective immunity
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Beste allen,

Wij krijgen intern een nieuwsbrief, die we niet mogen verspreiden, maar ik zie niet in waarom ik het niet zou mogen delen met deze groep.
Verspreid het ajb niet verder.
Er staat interessante informatie onder het kopje "protective immunity and human coronaviruses". Let op, er zijn twee blokken tekst, een key
messages en een summary. Veel hiervan zal jullie wel bekend zijn.
Helaas heb ik geen tijd om de genoemde literatuur door te spitten.
Misschien jij wel [redacted]?

gr,
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****
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Subject: COVID-19 Literacy | for CIb internal use only

COVID-19 Literacy | for CIb internal use only

Jaargang 2020, Editie 2, 27 mei 2020

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Key messages from the literature on COVID-19

Introduction

This is the second edition of the COVID-literacy newsletter, in which we will regularly present key messages from the literature on COVID-19. The current newsletter contains an update on the topic Capacity of health care systems and several new topics.

Why?

Since March 2020, many of our colleagues at the Centre for Infectious Disease Control (Dutch: Centrum Infectieziektebestrijding – CIb) have been reviewing new literature on a wide range of subjects related to COVID-19 every week. These teams have developed living summaries for internal use, which serve as a foundational body of literature to support decision-makers (including the OMT), guideline developers, and researchers on COVID-19 within CIb. These summaries can also be used as a starting point for more specific literature searches.*

Looking to contribute?

If you would like to contribute to these literature teams, please let us know. We are always looking for new colleagues. Also, if you believe that a certain important topic is missing and that a new team should be set up, we are happy to look into this together. Please e-mail us at [redacted]@rivm.nl.

We hope you enjoy our summaries!

Best,

[redacted] [redacted], [redacted] [redacted], [redacted] [redacted], [redacted] [redacted] [redacted]

*The short summaries on topics related to COVID-19 presented in this weekly newsletter are based on quick searches in EPPImapper, as well as manual searches by authors on specific topics. Two researchers ([redacted] [redacted], [redacted] [redacted]) shared tasks related to study selection. The synthesis of results differs per topic, as is shown by the authors of each summary.

It is currently urgently necessary to identify the most important evidence quickly. This led us to opt for this quick approach, despite its inherent risk of overlooking key evidence or making misguided judgements. It takes our teams approximately two weeks to process and review studies after they are published. These living summaries will be updated with new information when relevant.

Key messages

COMMONLY REPORTED SYMPTOMS OF COVID-19 IN HOSPITALIZED PATIENTS

- To contain the spread of COVID-19 rapid detection of suspected cases is needed. Description of the occurrence of specific symptoms during the course of disease in groups of patients with various levels of severity of diseases can help to identify people with potential COVID-19 infection.
- Data from 14 studies showed a wide variance in the prevalence of symptoms at hospital admission due to differences in admission policies and lack of uniform registration of symptoms.
- At hospital admission the most commonly reported symptoms of COVID-19 were fever (> 38 °C) and coughing. Symptoms related to upper respiratory tract infection were less frequently reported as a reason for admission. Up to one third of patients had gastrointestinal complaints (abdominal pain or diarrhoea).
- Patients may present with nonspecific symptoms. More cohort data is needed to determine which symptoms occur simultaneously and could be associated with a complicated course of disease.

SYMPTOMS OF COVID-19 IN THE GENERAL POPULATION

- COVID-19 is associated with a variety of symptoms and complaints; in addition to the generally associated symptoms of fever, cough and shortness of breath, these also include shivering, general malaise, fatigue, ocular pain, muscle pain, headache, sore throat, stomach ache, pain when breathing, dizziness, rhinorrhea, a hoarse throat, general confusion, anorexia, diarrhea, vomiting, nausea, hyp-/anosmia, dysgeusia, conjunctivitis and skin problems.
- Frequencies of symptoms differ by study cohort.
- Anosmia, ageusia and fever are the symptoms strongest associated with a positive COVID-19 test compared to a negative COVID-19 test, according to the available literature.

LUNG ABNORMALITIES AMONG CHILDREN WITH COVID-19

- Children show various degrees of lung abnormalities on radiography; ranging from small patchy shadows to bilateral pneumonia.
- Lung abnormalities may be present regardless of severity of the disease and regardless of the presence of respiratory symptoms. However, the more severe the illness, the more severe the lung damage.
- Limited data suggests possibility of full recovery of the lungs.
- More research is necessary to understand lung damage among children and more research should look into recovery of lungs.

CAPACITY OF HEALTH SYSTEMS - UPDATE

Countries' (public) health systems are being challenged with the required surge capacity during the COVID-19 crisis such as:

- Difficulties to keep up with contact tracing as traditional manual procedures are not fast enough for SARS-CoV-2 , especially in international, high mobility and density populations . In addition, mild/moderate cases sent home risk households, increase community spread and make monitoring more challenging .
- The lack of objective and robust surveillance that maps the evolution of the epidemic and provide evidence to inform control approaches in advance is critical .
- Early diagnostic capacity also faced challenges due to an initial lack of positive control, personnel/time and a lack of primers and/or probes
- Shortages have been a critical challenge to health systems, especially in epicenters ,

with absence of testing, available ICU beds , personnel and PPE . Furthermore, long-term escalation of health care place pressures on workers, affecting their physical and mental health [5,16], and compromising the clinical management of patients .

- Overwhelmed hospitals cannot provide adequate care and isolation for mild and moderate cases .

The included papers describe strategies to address these different challenges based on countries experiences, case studies, and expert opinion and advise.

POINTS OF ENTRY

- The majority of papers studying the impact of transport on the spreading of COVID-19 are modelling studies assessing the impact of air travel.
- The outbreaks on cruise ships were a valuable source of information about general characteristics of the virus.
- Literature about spreading of COVID-19 via maritime or land-transport is minimally available.
- There is a lack of information from local procedures, gaps, needs and best practices of points of entry in their COVID-19 response.

PROTECTIVE IMMUNITY AND HUMAN CORONAVIRUSES

- Infection with hCoV-229E (human alpha coronavirus) does not lead to protective immunity, but severity of disease is significantly lower upon re-infection.
- Seasonal hCoV can frequently cause re-infections, after as little as 12 months post-infection.
- Most people that recover from SARS-CoV-2 infection have antibodies to the virus, however some have very low levels of neutralizing antibodies.
- Memory T-cells for SARS-CoV shown to have lasted for several years, whereas neutralizing antibodies to SARS-CoV and to MERS partially wane over time.
- There is probably no significant neutralizing cross-reactivity between SARS-CoV-2 antibodies and other hCoV antibodies, but there may be cross-stimulation with other hCoV.

AEROGENIC TRANSMISSION OF SARS-COV-2

- Multiple parties, including the Ministry of Health, Welfare and Sport, asked the RIVM for advice about aerogenic transmission of SARS-CoV-2 over a longer distance than 1,5 meters and possible implications for ventilation inside buildings.
- Aerosols are formed during speech, coughing and sneezing. However, at this moment there is not enough evidence that aerogenic transmission plays a relevant role in the spreading of SARS-CoV-2.
- Based on the current insights, alterations to ventilation systems are not necessary. Current guidelines for ventilation can be used.
- There will be a separate advice on the role of aerosols in singing and sports.

EFFECTS OF NON-PHARMACEUTICAL INTERVENTIONS

- Non-pharmaceutical interventions, such as social distancing of all or of risk groups only, with or without school and/or business closure, testing and quarantaine of suspect cases have positive effects on the containment of the COVID-19 outbreak. Their separate effects are difficult to disentangle.
- All these interventions vary in their (estimated) effectiveness due to differences in settings, adherence and model assumptions.
- Early models assessing the impact of the epidemic on health care resources were based on Chinese parameters, including a shorter ICU stay than in Europe.
- Adherence to social distancing and other non-pharmaceutical interventions is probably higher in China which affects estimates of efficacy.

PERSONAL PROTECTION EQUIPMENT (PPE) USE BY THE PUBLIC

- Personal protection equipment for the public refers almost exclusively to (face) mask use.
- Mask use is associated with a slightly (6%) to considerably (47%) reduced risk of developing respiratory infections.
- Mask use seems more effective in some Asian countries where mask use has been common practice/mandated with earlier outbreaks.
- Recommendations vary across countries in Europe. These differences are partly motivated by fear of shortages for medical staff and of improper use that might increase

the infection risk.

Summaries

COMMONLY REPORTED SYMPTOMS OF COVID-19 IN HOSPITALIZED PATIENTS

Research questions & methods

What are commonly reported symptoms of COVID-19 in hospitalized patients?

LitCovid/EPPImapper were screened to identify multicenter studies on cohorts of hospitalized COVID-19 patients (≥ 100 patients).

Results

In the last edition of the Newsletter we reported about underlying conditions and the risk of severe illness in patients that were admitted to the hospital or the ICU. This time we summarize the findings from hospital studies that described the symptoms in COVID-19 confirmed patients at admission.

Research and patient characteristics

14 studies reporting on symptoms of COVID-19 were identified: from China (1-10), the USA (11-13), and the Netherlands (14). The studies comprised 100-5700 patients, with a median age of 47-72 years. In all cohorts most patients were male (52-67%). In the studies 38-90% of the patients had mild disease at admission and consequently, severity may not have been the most important reason for admission. Another reason may have been isolation of cases.

Commonly reported symptoms

Most commonly fever and cough were reported, but not all patients presented with symptoms related to a respiratory tract infection. Especially symptoms related to upper respiratory tract infection (nasal congestion/rhinorrhea, throat ache) were less frequent than cough or dyspnea. Gastrointestinal symptoms were even less frequent. Unknown is whether these symptoms coincided at the moment of admission or whether specific symptoms were related to severity of disease.

The prevalence of symptoms varied widely between studies, and the biggest range was found for dyspnea: 5-70%. These data must be interpreted taking into account differences in admission policy and lack of uniform registration of symptoms. One study performed a multivariable analysis and found that dyspnea was an independent risk factor for mortality (HR: 3.96; 95% CI: 1.42-11). The studies did not report about more rare manifestations of disease such as cutaneous manifestations (15), neurological symptoms (16), conjunctivitis (17), anosmia or ageusia (18).

Table. Reported symptoms of patients at admission in 14 multicentre studies (1-14)

Symptoms	**Reported prevalence**
Fever (> 38 °C)	31-61%
Cough	32-79%
Dyspnoea	5-70%
Throat ache	11-14%
Myalgia	12-31%
Sputum production	13-43%
Nausea/vomiting	1-19%
Diarrhoea	3-24%
Nasal complains*	5-6%
Abdominal pain	2-33%

* = nasal congestion/rhinorrhoea

Conclusion

The first cohorts of patients presenting to hospitals with suspected COVID-19 frequently had symptoms related to respiratory tract infection, but also gastrointestinal complaints were reported in up to one third of patients. Not all cases presented with fever. In these studies some patients presented with nonspecific symptoms to hospitals, complicating the accurate detection of cases. More research reporting on the frequency of concurrent symptoms is needed in addition to defining combinations of symptoms that may be indicators of COVID-19 infection.

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SYMPTOMS OF COVID-19 IN THE GENERAL POPULATION

Research question & methodology

Four studies that compared symptoms in SARS-CoV-2 positive and negative persons were selected after a search using EPPI-mapper (*). We selected studies from peer-reviewed journals, in English or Dutch, with ³ 200 participants including community-based and non-hospitalized SARS-COV-2 cases, and providing information about COVID-19 symptoms.

Results

Gudbjartsson et al. studied two Icelandic cohorts . One cohort consisted of 10,797 persons from the general population of whom 87 were tested positive for SARS-COV-2. The second cohort was a random sampling cohort of 2283 people of whom 13 tested positive. Of these cohorts, 57% of the positive cases experienced symptoms, and 29% of the negative cases. Reported symptoms were: fever, coughing, overall pain, headache, a sore throat, rhinorrhea, fatigue, anosmia and ageusia. Symptoms were reported more frequently by positive cases. Statistical significance was not calculated between groups.

In a Dutch study , 803 healthcare workers were tested and surveyed on their symptoms. Ninety positive cases for SARS-COV-2 were compared with 713 negative cases. Symptoms that were most frequently reported among positive cases were: headaches, general malaise, muscle pains. Among negative cases, these were coughing, sore throat and rhinorrhea. Univariable analysis indicateed that general, non-respiratory symptoms (anosmia, muscle pain, ocular pain, general malaise, headache, fatigue and fever) were reported most frequently among positive cases. Anosmia was strongest associated with SARS-COV-2 (OR=23; 95% CI 8.2-65). This study's data were used to develop a prediction model in which the seven most reported non-respiratory symptoms were included. Anosmia and muscle pain received extra weight. This model showed 91% sensitivity and 56% specificity (ROC 0.78).

A study performed in the USA and the UK compared persons with a positive and negative test for SARS-COV-2 and their symptoms reported in a health tracking app. The 6,452 positively tested persons and 9,186 negatively tested persons in the USA were compared with 726 positively and 2,037 negatively tested persons from the UK. These cohorts were compared for symptoms of anosmia, ageusia, fever, prolonged coughing, fatigue, shortness of breath, diarrhea, general confusion, anorexia, stomach ache, a hoarse throat, chest pain. Anosmia was reported more frequently among positively tested persons (OR = 6.7, 95% CI = 6.3 – 7.2; P<0,0001). The combination of age, sex, anosmia/ageusia, fatigue, prolonged coughing and loss of appetite resulted in a model with a sensitivity of 65% and a specificity of 78% (ROC 0.76).

In Roland et al., a change in smell and taste, fever and muscle pain were associated with a positive SARS-CoV-2 test (n=154) . Shortness of breath and a sore throat were associated with a negative test (n=157). The prediction model based on these five symptoms resulted in a predictive value of 82%.

NB: A more extensive review of symptoms associated with the severity of outcomes and infectiousness is performed as preparation for the outbreak management team meeting of 25 May 2020. The full report and the review will be published online very soon.

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LUNG ABNORMALITIES AMONG CHILDREN WITH COVID-19

Research questions & methods

What is known about children with COVID-19 and lung abnormalities?

Inclusion criteria: English/Dutch studies with quantitative data on lung abnormalities among children with COVID-19.

Results

Lung abnormalities

In the 19 studies, between 22%-100% of pediatric cases with COVID-19 showed lung abnormalities. Within this group, between 0%-100% reported no respiratory symptoms. Between 0-100% showed unilateral lung involvement and 0%-75% showed bilateral lung involvement (1-16). Ground glass like opacities (GGO) (25%-100%), local patchy shadows/mottling (19%-75%), and consolidation (0%-75%) were most seen (1-16).

Recovery of lung damage has been reported in two studies. Full lung recovery ranged between 33% and 100% (10, 13).

Severity of disease and lung damage

Lung abnormalities were seen in asymptomatic, mild/moderate, and severely/critically ill children with COVID-19 (1,2,9,10,12). Studies found lung abnormalities in between 20%-66% of the asymptomatic cases (9,12, 17) with GGO and patchy shadows most often reported. Severe/critical pediatric cases frequently had bilateral lung involvement and pneumonia (15, 18).

So far, no severely ill child has been reported without lung abnormality, only among asymptomatic and mild/moderate pediatric cases (2,3,5-9,11-13,16,17).

Lung Ultrasound (LUS)

Denina et al (2020) compared LUS results with radiography results (19). The study (n=8) found that LUS had in 7/8 cases similar results. One case had a normal CT-scan and an interstitial pattern on the LUS. LUS use may be preferred because it reduces radiation exposure, and it can be taken to the patient instead of moving the (infectious) patient within the hospital.

Conclusion

It seems that children with COVID-19 may show lung abnormalities, regardless of the severity of the disease and type of symptoms. However, lung abnormalities are more common and more severe among severe/critical cases. Full recovery of the lungs has been observed, this may be dependent on the damage in the lungs and data is limited. Most research had a sample size of n<11, thus cautious interpretation is necessary. More research is required to better understand lung damage and recovery among children. Lastly, LUS could potentially be easier in use, less damaging, and as effective as radiography.

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CAPACITY OF HEALTH SYSTEMS - UPDATE

Research questions & methods

- How to manage increasing surge and demand for health system due to COVID-19?
  - What are the challenges and potential solutions to address these challenges?
- Exclusion Criteria:
  - Non-peer reviewed papers; papers not based on the COVID-19 experience; papers that are merely descriptive of the response without answering the research question.

Results: Strategies for handling the increased demand from health systems to respond to COVID-19

Supporting the efficient implementation of response measures

- Through contact tracing
  - By using a mobile phone App, contact tracing and notification can be made instantaneous upon case confirmation, by alerting recent close contacts of diagnosed cases and prompt them to self-isolate [1, 11].
- Through surveillance systems
  - Adding repeated random surveys can generate a robust evidence base for decision- making on community control and health resource allocation .
- Though travel control
  - Control of entering travelers with imposed quarantine and deny entry to non-local visitors .
- Through learning lessons from previous epidemics
  - Intragovernmental coordination drawing from experiences of SARS, H5N1 and H1N1, with inter-ministerial coordination .

Increasing testing capacity by

- Triage based on clinical case definition or presumptive diagnosis ; tracking based on risk level; and mobile hotline developed for reporting suspicious symptoms .
- Readjust surveillance systems and develop national laboratory networks to produce diagnostic tests .

Upholding hospital capacity and shortages

- For emergency care units
  - ○ Rapidly convert general beds to ICU beds and general hospitals to critical care hospitals ; cohorted ICU with proximity to emergency department .
  - ○ Transfer health care professionals and equipment to the most affected area (epicenters) [3,11].
  - ○ Avoid unauthorized moving of personnel across departments, especially ones with high risk or vulnerable patients [8,9]; screening for entry and exit (such as temperature checks) and specific rooms for donning and doffing of PPE .
- For personal protection equipment
  - ○ Clear guidance form government on the usage, standards, and stock management [3,6,8], with rapid action and regional production [3,11].
- For human resources
  - ○ Simple guidance for non-infectious disease specialists working on COVID-19 ; training and adherence to IPC measures [4,6,8], implemented in all departments of hospitals [9,10].
  - ○ Adjusting health care workers working hours with adequate rest, meal time, and provision of healthy meals [6,8].
- For health care delivery facilities
  - ○ Fever clinics adjacent to hospitals to decrease cross contamination [6,7].
  - ○ Technology and digitalization for outpatient services as apps and web services for booking appointment; robots to perform basic tasks (such as moving supplies between pharmacy and hospital rooms) .
  - ○ 'Ark hospitals' (temporary hospitals) built by converting public venues, such as stadiums to isolate patients with mild to moderate symptoms while providing medical care, disease monitoring, food, shelter, and social activities [12-15].
  - ○ Algorithms used to manage patients flows in and out of field hospitals, and between areas [12,14].

Conclusion

From these studies we can conclude that:

1. Control measures have profound and long-lasting negative effects on society and economy, but when effective, they ensure health systems can keep up with the increased surge and ultimately save lives .
2. Using a mobile phone App for contact tracing should be one tool among many general preventative measures such as physical distancing, hand and respiratory hygiene, and regular decontamination .
3. Collaboration between public health and animal health structures can be useful for developing new tools/approaches and to support evidence-based policy- making .
4. While molecular testing for SARS-CoV-2 was quickly implemented in EU/EEA, clinical validation of specificity and sensitivity, can be improved. Capability testing based on proficiency panels is needed .
5. Hospital wide COVID-19 committee should be initiated to formulate procedures and

policies that are dynamic and open to change based on emergency knowledge on COVID-19 and the situation at the hospital. At peak of epidemic, data suggests that hospitals should prepare for at least 4-5 times increase in ICU capacity compared to baseline [7,8,17].

6. Great emphasis should be placed on staff training and standards for PPE and IPC in health facilities, as well as the well-being of health care workers [6,8].
7. The risk of infection and cross contamination required hospitals to quickly adapt their practices and management of outpatient services. Ark hospitals help spare regular hospitals from becoming quickly overwhelmed [12,14], allowing for monitoring of mild and moderate cases and their isolation. Extra benefits are seen since these facilities can be constructed rapidly, in massive scale and low cost [13,15]. Preliminary data indicates that 'ark hospitals' are correlated with reductions in new cases and field hospital deaths .

Most of the results are based on expert opinion and/or small case studies within specific contexts (one hospital) and areas (one county). More representative studies are needed to support the generalization of findings.

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POINTS OF ENTRY

Research questions & methods

In addition to the searches that are generally performed as elaborated upon (*), we included studies selected by the JA Healthy Gateways on 25th of May 2020 (https://www.healthygateways.eu/Novel-coronavirus).

The main question of this first review is to get an overview of the available literature that assesses the impact of international travel on the COVID-19 pandemic. This overview is used to decide on subsequent, more detailed reviews and to guide the direction of future research. We excluded studies solely based on the first Chinese disease data, studies focusing on an economic perspective only, studies presenting no new data or analysis, or in languages other than English, French or German.

Results

We identified 73 studies, of which 14 were excluded. The majority of studies assessed the impact of air travel on the initial spreading of the disease. These were mainly modelling studies using air travel data and first assumption on R0, prevalence to predict the impact for a specific country, continent or in general [1-7]. One study described transmission during transport . One study derived a travel vulnerability index based on these data, to guide future risk on introduction of COVID-19 . The other large set of studies, predicts the impact of travel restrictions and border control measures to this international spreading of disease [10-19]. The effect of entry- and exit screening has been extensively reviewed before this COVID-19 pandemic , studies focused on COVID-19 confirm that these only delay the introduction of disease, but cannot prevent it [21-33]. Liu et al. indicate, however, that cases identified during entry-screening did not lead to secondary cases .

For maritime travel, we only identified studies assessing outbreaks on cruise ships. Studies assess the reproductive number , the transmission routes [36, 37], application of public health measures [38-41], ethical considerations . Also, this isolated outbreak is used to deduce characteristics applicable to COVID-19 management in general [43-48]. Only one study assessed an outbreak on cargo ships .

Only two studies involved ground transport in their analysis, and these only focused on introduction of cases into other regions in China [50, 51]. Transmission during ground-transport was not assessed.

Conclusion

From this first overview, we can conclude that the majority of papers studying the impact of transport on the spreading of COVID-19 are modelling studies assessing the impact of air travel. The outbreaks on cruise ships were a valuable source of information about general characteristics of the virus. Profound knowledge on the spreading of COVID-19 via maritime or land-transport is minimal. And there is a lack of information from local procedures, gaps, needs and best practices of points of entry in their COVID-19 response. Subsequent reviews will dive into these sub-topics with more detail.

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PROTECTIVE IMMUNITY AND HUMAN CORONAVIRUSES

Research questions & methods

The main question is if there is immunity to SARS-CoV-2 after an infection and if yes, how long does it last. At the moment this is not known, but other information is available:

1. Is there immunity after (non SARS-CoV-2) HCoV infections and / or is there a difference in severity of disease in re-infection with other HcoV?
2. What is the pattern of antibody response in HCoV infections? Is there evidence for immunity due to (neutralizing) antibodies after HCoV infection?
3. Is there evidence for cellular immunity?
4. Is there crossreactivity between coronaviruses?

The overview is not conclusive and more literature still needs be added. There is a lot of literature about this topic. As a starting point for this overview, these overviews were used: (1-3). More publications and prepublications were added after screening PubMed, BioRxiv and MedRxiv.

Results

1. Is there immunity after (non SARS-CoV-2) HCoV infections and / or is there a difference in severity of disease in re-infection with other HcoV?

In a study in 1990 15 volunteers were challenged with HCoV-229E and 10 of them got infected.

One year later 9 of the 10 infected patients got re-challenged and 6 of them got infected (4). None of the re-infected showed any symptoms (4). In a study in 1984 six volunteers were experimentally infected with HCoV TO: all 6 developed symptoms and detectable virus and 5 of 6 experienced significant rise in titer -> Re-challenged 8-12 months later -> 0/6 experienced illness, detectable virus or significant rise in titer (5). In 1990 it was found that that lower proportions of individuals with high neutralizing titer against HCoV-229E experienced 'significant colds' upon viral challenge compared to individuals with low titers (6).

A new study was pre-published, following 10 subjects over 35 years (1985-2020), showing that protective immunity to seasonal hCoV was very short with frequent reinfections at 12 months post-infection and substantial antibody reduction at 6-12 months(7).

I could not find re-infection data on SARS-CoV-1 or MERS.

2. What is the pattern of antibody response in HCoV infections? Is there evidence for immunity due to (neutralizing) antibodies after HCoV infection?

Significant antibody level rises against HCoV-229E correlated well with symptoms, clinical score and virus shedding (8). It was observed that higher serum levels of specific IgA and IgG protect from HCoV-229E infection -> 15 volunteers were challenged with virus and the 10 volunteers that got infected had lower IgA titers (4).

For MERS it was found that severe cases tended to have higher antibody responses compared to mild cases. MERS antibodies decreased throughout the 6 months following disease onset. Antibody titers in 4 of 6 mild cases were undetectable (9). 3 asymptomatic MERS patients did not seroconvert within 3 weeks (confirmed positive by RT-PCR) and for the remaining patients the seroconversion rate gradually increased with increasing disease severity. 75% of deceased patients did not seroconvert by week 3, compared to 0% of survivors (10). One year after MERS infection IgG antibodies were detectable and maintained in all severe (n=5) and in most non-severe (n=6) cases, though some lacked detectable neutralizing antibodies (Nab). Antibody responses tended to be higher among severe cases (11). Maybe there is a dependence on severity of disease for MERS-CoV infections (at least for Ab levels, not clear for immunity). Antibodies detected at month 18 in 2 of 9 patients with severe symptoms. More variable antibody longevity among patients with milder symptoms (12).

Nab against SARS-CoV-1 remained stable for 7 months (13). 100 % of patients from this study (14)were seropositive for SARS-CoV-1 until month 16. Titers peaked at month 4. IgG and neutralizing antibodies were undetectable in 19.4 % and 11.1% of serum samples, respectively, at month 30 and in 25.8% and 16.1 %, respectively, at month 36 (14).

For SARS-CoV-2 there is indication that humoral response is not the sole mechanism to achieve immunity for SARS-CoV-2: about 30% of recovered patients generated a very low level of NAb titers (ID50: <500) and Nab of 10 patients are below the limit of detection (all are PCR pos.) -> 2 week follow-up showed no major differences -> all done with pseudovirus neutralization assay: Nab of elderly and middle-aged patients were significantly higher than of young patients (p<0.0001 and p<0.0001, t test) the corresponding median ID50s were 1537, 1255, and 488 (15). Seroconversion of 50 % of SARS-CoV-2 patients occurred by day 7 and in all by day 14: all patients showed detectable Nab. The titers did not suggest close correlation with clinical course (16).

Many more publications about antibody responses can be found in the supplementary material in (1).

3. Is there evidence for cellular immunity?

Indication that memory T-cells for SARS-CoV-1 lasted at least 2 years. Study demonstrated that both CD4+ and CD8+ T-cells are involved in SARS-CoV-1 N-specific memory immunity and that the memory T-cell responses specific for SARS-CoV-1 have been maintained for 2 years in absence of antigen (17)and even longer (18). See also (2)for a comprehensive summary. Indication that Th1 type response is key to successful control of SARS-CoV and MERS-CoV and speculatively also the case for SARS-CoV-2 (19, 20).

4. Is there crossreactivity between coronaviruses?

Infections with HCoV-OC43 and HCoV-229E did not lead to antibodies (acute or convalescent phase) against SARS-CoV by IFA or neutralization (13).

Results on differential recombinant immunofluorescence assay indicated cross-reactivity or cross-stimulation against the four endemic human coronaviruses in several patients (16). Monoclonal antibodies raised to SARS-CoV RBD did not bind the MERS-CoV RBD even at high concentrations (10ug/mL) and all had low or no neutralizing activity against MERS-CoV pseudovirus (21).

The absence of SARS-CoV-2 antibody cross-reactivity with RBDs from SARS-CoV and MERS-CoV is surprising because based on the sequential and structural similarities of RBDs from SARS-CoV-2 and SARS-CoV, they predicted some degree of cross-binding and even cross-neutralization between the two viruses (22). Sera from recalled SARS patients could neutralize SARS-CoV, but not the SARS-CoV-2 pseudotyped lentiviruses (23).

Conclusion

There is probably no significant neutralizing cross-reactivity between other human Coronaviruses and SARS-CoV-2. Not every infected person develops neutralizing antibodies after SARS-CoV-2 infection and there may be a correlation with the age of the patients. Once neutralizing antibodies are produced, they will probably decrease over time, but that does not equal that immunity has to wane over time. This is not known at the moment.

In order to assess findings reliably further research is still needed, especially longitudinal studies to determine whether immunity after infection is protective and if yes for how long. Further questions are whether immunity is sterile and if there is a risk for antibody-dependent enhancement.

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AEROGENIC TRANSMISSION OF SARS-COV-2

Research questions & methods

Can SARS-CoV-2 be transmitted through aerosols? If so, are there any additional measures necessary for ventilation systems? To answer these questions, relevant literature was searched through databases like PubMed and Embase. Only studies regarding SARS-CoV-2 were included. Literature specifically on singing, exercise and fecal-oral transmission was not included.

Results

Aerosols are formed during speech, coughing and sneezing (Asadi et al., 2020). Under laboratory circumstances it has been shown that SARS-CoV-2 can survive in aerosols for several hours (Fears et al., 2020; Van Doremalen et al., 2020). However, an R_0 of 2-4 does not indicate aerogenic transmission. Different studies within hospitals have found virus RNA in air samples (Liu et al., 2020; Ong et al., 2020; Santarpia et al., 2020). In contrast, two other studies did not find RNA in air samples, even when taken close to a patient's chin (Cheng et al., 2020; Faridi et al., 2020). In some occasions outside the hospital aerogenic transmission is named as a possible transmission route (Brurberg, 2020; Lu et al., 2020; Wang et al., 2020). However, in these studies other transmission routes cannot be excluded. There are no studies that have measured the presence of virus in the air in public spaces, such as schools and supermarkets. Research on the outbreak aboard the Diamond Princess cruise ship showed that transmission took place via direct contact and contaminated surfaces, and not through the air-conditioning system (Xu et al., 2020).

Conclusion

Different studies based on epidemiologic, virologic and modelling research do not show aerogenic transmission as a main route for the spread of SARS-CoV-2. Therefore, at this moment there is not enough evidence that aerogenic transmission plays a relevant role in the spread of SARS-CoV-2 over longer distances. Based on the current insights, alterations to ventilation systems are not necessary. Current guidelines for ventilation can be used. The background document about this subject is published on the RIVM website.

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EFFECTS OF NON-PHARMACEUTICAL INTERVENTIONS

Research questions

- What non-pharmaceutical interventions are effective and feasible, and could also be of use in the context of the Netherlands?
- What non-pharmaceutical interventions are effective and feasible in the context of the COVID-19 epidemic in China?

Results

Most studies, and all Chinese studies, that are summarized are based on models, to assess the effect of the interventions on various outcome measures. Country and regional estimates of effectiveness vary due to different healthcare systems, criteria for ICU admission and discharge, age distribution and contact patterns in society, adherence and other medical, sociological and economical characteristics. The actual phase of the epidemic at implementation also affects these estimates. Another complicating factor is that interventions were often introduced simultaneously.

Studies relevant for the context of the Netherlands

Overall, the various non-pharmaceutical interventions had positive effects on the containment of the outbreak. Quarantine of people exposed to confirmed or suspected cases averted between 41% to 81% of cases and between 31% to 63%, compared to no measures (1). Physical distancing measures resulted in a contact reduction of 78% in British Columbia. Home isolation of suspect cases, home quarantine of household members and social distancing limited to risk groups might reduce the deaths by half in the US and UK (2). Whereas household isolation or mandated social distancing, including closures of schools and non-essential business, can reduce the number of deaths by at least 50%, as calculated for the Swedish setting (3). Recent modelling of school closures alone, in China, predicted a prevention of only 2-4% of the deaths (4). The response time of the country had an impact too: countries reacting late had an increase in mortality, 23 days after the first COVID-19 death there were 2.5 times more deaths in late reacting countries than in early reacting countries (5).

Two assessed papers studied the options for exit strategies. In one strategy, the Netherlands was divided into 10 parts. In general, every 90 days, one part had a measure lift. On average, individuals will experience 432 days of intensive control. In this manner, the number of cases would remain within the limits of the Dutch health care capacity. At the end of the epidemic, 56% of the population has become immune (6). Another strategy proposed was to alternate social distancing measures between, 78% contact reduction, and 20% contact reduction, every three or four weeks until August 2020. This allowed an overall continued decline in the number of cases (7).

An Israelian survey revealed that when compensation for loss of income due to self-quarantine was assumed, the self-estimated compliance was 94%, but without compensation this dropped to less than 57% (8).

Studies relevant for the context of China

Various non-pharmaceutical interventions have been studied in the context of China. Overall, the lockdown in China was effective in preventing the spread of COVID-19 (9). The lockdown in China reduced the doubling time of the outbreak from 2 days to 4 days (10). After January 30, various regions went from a reproduction number higher than one, to an R<1 (9). The Wuhan travel ban resulted in a delayed arrival time of COVID-19 in other cities by approximately 2.91 days. This delay provided extra time to prepare (11). However, early detection and isolation with social distancing prevented more infections than travel restrictions and contact reductions, one study found that no early detection and isolation resulted in a 5-fold increase in number of cases, whereas no travel restrictions resulted in a 2.6-fold increase in number of cases (12). Cities that responded earlier with control measures reported 33.3% fewer confirmed cases during the first outbreak week compared to cities that started control later (11).

Adherence to these measures in China is probably higher than in the Netherlands, due to stronger law enforcement. The one to two children policy (Viner), high population density in the cities and widespread mask use might affect the effect of these interventions as well (13). Furthermore many of these papers evaluate the beginning of the epidemic, with higher R0 and less accurate model parameters. These parameters were initially used in papers estimating the epidemic in other countries as well, e.g. an average ICU stay of ten days (2)whereas this appeared to be 2-4 weeks in the Netherlands.

Conclusion

Regarding the evidence from other studies, the strict isolation measures implemented in the Netherlands and the compensation for loss of income seems a good policy in preventing COVID-19 cases and deaths. The studies performed in the context of China should be thoughtfully interpreted when translating it to the context in the Netherlands. More data is necessary make a conclusion on feasible exit strategies.

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PERSONAL PROTECTION EQUIPMENT (PPE) USE BY THE PUBLIC

Research question & methods

Recommendations for mask use by the public vary across countries, ranging from no recommendations to mandatory mask use relatively crowded settings(1). Dutch guidelines have recently included mask use to allow increased use of public transport. What is the evidence on this, much debated, measure?

Three recent reviews evaluated the evidence for use of masks by the public. A limited number of other papers evaluated community mask use in Asia whereas one study estimated the impact of mask use in the USA.

Results

The ECDC concludes in her review that the use of masks may serve as a means of source control, from asymptomatic individuals, but the contribution to the decrease in transmission is unknown(2). Brainard et al concluded that in 3/12 RCTs a mask very slightly reduced the odds of developing influenza like illness (6%), but more so in observational studies(3). Masks were consistently protective in the general community, schools and universities, and for visits to healthcare clinics, albeit not always significant. Liang et al concluded that mask use reduced the risk of respiratory virus infection by 47%(4). The latter review also included papers on SARS.

Eikenberry et al modeled the potential impact of mask use in Washington and New York state and concluded that broad adoption of even relatively ineffective masks may reduce transmission(5). However, they used high doubling times, reflecting the beginning of the epidemic, without e.g. social distancing.

The ECDC stresses that masks should only be considered as a complementary measures to social distancing, etc. Recommendations on community mask use should take into account evidence gaps, the supply situation, and potential negative side effects. Hongkong residents are used to wearing masks when needed and compliance on the street was 96.6%(6), but 13.0% used them wrongly (7). Eleven clusters (113 persons) in Hongkong were associated with mask-off settings (dining, drinking, singing, exercising) and only 3 clusters (11 persons), in workplace 'mask-on' settings(6).

Conclusion

There is enough evidence to support the use of masks for short periods of time when in transient higher risk situations. Monitoring of proper use and potential negative effects is, however, important.

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