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RIVM 144-2020 DG

25/08/2020

Cc:

RIVM
[redacted]
Postbus 1
3720 BA Bilthoven
CC: Annex F

- URGENT EN VERTROUWELIJK -

Onderwerp: Verhoging van luchtvochtigheid in gezamenlijke ruimtes essentieel vanaf week 44

Naarden, 20 Augustus 2020

SAMENVATTING

- Nederlandse studie bevestigt grote rol aerosols bij verspreiding van Influenza en Sars-CoV-2;
- Aerosol-concentratie wordt bepaald door Specifieke Luchtvochtigheid (q);
- Lagere Specifieke Luchtvochtigheid (q < 6 g/kg) leidt tot exponentiele verspreiding;
- Hogere Specifieke Luchtvochtigheid (q > 8 g/kg) beperkt verspreiding met 591%;
- Airco's dragen bij aan verspreiding door evaporatie van respiratoire druppels';
- Tot week 44 zijn de huidige maatregelen (Hygiëne en Social Distancing) voldoende;
- Prognose: explosieve toename R0 vanaf week 44 (eind oktober) bij huidige maatregelen;
- Zuidoost-Nederland zal als eerste getroffen worden. Noord-Nederland als laatste;
- Vanaf week 44 zijn de huidige maatregelen (Hygiëne en Social Distancing) onvoldoende;
- De huidige maatregelen zullen een 'lock-down', medio November tot April, niet voorkomen;
- Verhoging van Specifieke Luchtvochtigheid (q) in ruimten zeer effectieve bestrijdingsmethode;
- Vanaf week 44 is luchtbevochtiging van essentieel belang omdat aerosols voornamelijk verantwoordelijk zullen zijn voor de verspreiding van Influenza en Sars-CoV-2.

INLEIDING

Uwe Majesteit,
Uwe Excellenties,
Hoogedelachtbare heer en vrouwe burgemeester,
Weledelgestrenge heer en vrouwe burgemeesters,
Hooggeleerde heer en vrouwe,

Ik schrijf u na het optekenen van enkele zeer belangrijke conclusies, in een Research Paper, na een 5 maanden durend onderzoek (Annex B) waar ik leiding aan heb gegeven. Ten grondslag aan dit onderzoek ligt data, verkregen van het RIVM, KNMI, NIVEL en CBS. Twee teams hebben, onafhankelijk van elkaar, studies gedaan naar eventuele causale effecten van het weer (regen, zonlicht, wind, temperatuur, luchtdruk en luchtvochtigheid) op de verspreiding van de respiratoire virussen, Influenza A en Sars-Cov-2. Zo is er, bijvoorbeeld, met data van Nivel gekeken naar Influenza A in de jaren 2015 tot en met 2019.

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Onze research paper (Annex B), dat is aangeboden voor publicatie in *The British Medical Journal* (bmj.com), samen met alle data van bovengenoemde organisaties, zal derden in staat stellen om een *peer-review* te doen van onze bevindingen. De verwachting is dat *peer-reviews* onze bevindingen zullen bevestigen. Onze beide teams kwamen, onafhankelijk van elkaar, tot exact dezelfde conclusie.

Hetgeen wij geconstateerd hebben, is dat een lage luchtvochtigheid (95% zekerheid) direct bijdraagt aan de verspreiding van deze respiratoire virussen. Ons onderzoek heeft ons doen concluderen dat een lagere luchtvochtigheid lineair tot een hogere evaporatie van respiratoire druppels (diameter 5-10 micron) leidt. Door evaporatie ontstaan de zogenaamde micro druppels ("aerosols" met een diameter minder dan 5 micron). Deze aerosols zijn bij een zeer lage luchtvochtigheid verantwoordelijk voor minimaal 50% van de COVID-19 gevallen. Onze conclusies worden feitelijk bevestigd door twee eerdere studies van het RIVM uit 2010 (Annex C en Annex D).

CONCLUSIE

Bij iedere verlaging van 1 g/kg specifieke luchtvochtigheid (q) treden er 5% meer besmettingen op. Bij een specifieke luchtvochtigheid (q) van 2 g/kg is de verspreiding en factor 6 keer groter dan bij een specifieke luchtvochtigheid (q) hoger dan 8 g/kg. De onderbouwing hiervan kunt u lezen in de bijgevoegde Research Paper.

Samengevat: Droge lucht leidt tot een versnelde evaporatie van respiratoire druppels. Deze evaporatie is verantwoordelijk voor de vorming van aerosols. Aerosols zijn verantwoordelijk voor 50% van de Influenza infecties (Bron; RIVM). De aanhoudende droge lucht, vanaf medio week 44 (oktober) 2020, zal leiden tot een exponentiele verspreiding van Sars-CoV-2. Deze droge lucht zal aanhouden tot medio week 11 (maart) 2021. Presymptomatische en symptomatische Sars-CoV-2 dragers, waaronder kinderen (Annex E), verspreiden het virus binnen 2-4 dagen na besmetting (bron: RIVM).

WAAROM HET INFLUENZA ONDERZOEK RELEVANT IS

Verspreiding van respiratoire virussen is zeer complex. Vele factoren hebben invloed. Niet in de laatste plaats; (verplaatsings)gedrag van de populatie. Het effect van maatregelen, zoals hygiëne en 'social distancing' hebben een direct effect. Onderzoek naar Influenza stelde ons in staat om – met hulp van het CBS – een 'base-line modelwaarde' vast te stellen waarbij gedrag van de populatie geen invloed had. Dit bleek, volgens data van het CBS, vrijwel gelijk gedurende die jaren. Oftewel; het maandelijkse verplaatsingsgedrag van de populatie blijkt nauwelijks te veranderen. Hierdoor was invloed van het weer op verspreiding van respiratoire virussen nauwkeuriger vast te stellen. Daar komt bij dat data van Nivel op dezelfde wijze wordt gecollecteerd (o.a. zelfde testvolume).

EERSTE STM PROEFMODEL IN MEI GETEST

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UITLEG STM – [redacted]

"The value added of the spatio-temporal model (STM) above correlation: We are taking into account the regional (sub-national) differences of humidity, besides the trends in COVID-19 in each region. And with a STM, we are not only estimating a correlation coefficient, we are actually finding how much risk is (was) reduced by the increase in humidity in The Netherlands, and we also identified, after taking into account humidity, which sub-national regions are riskier in terms of spread of COVID-19 (the bible belt). Simply put: The STM takes into account the regional differences in COVID-19, as well as the time trends of COVID-19 in each region".

MOGELIJKE ROL VAN VENTILATIE SYSTEMEN

Criticasters van het huidige beleid wijzen op de rol van ventilatiesystemen bij de verspreiding van aerosols. Er wordt verwezen naar de rol van een ventilatiesystemen als zijnde de bron van circulatie van aerosols door besloten ruimtes. Daar is onvoldoende causaal bewijs voor. Er is echter wel causaal bewijs voor de rol van airco's op de evaporatie van respiratoire druppels.

Airco's onttrekken, door het gebruik van zogenaamde "Evaporator Coils", warme lucht aan een ruimte. Zoals meteorologen kunnen bevestigen houdt warme lucht meer waterdamp vast dan droge lucht. Door de evaporerende werking dragen Airco's bij aan het ontstaan van aerosols, niet per definitie het verspreiden van aerosols.

***PEER-REVIEW* DOOR HET RIVM**

Op 18 maart had ik contact [redacted] (RIVM). Op 19 maart, in reactie op zijn e-mail, gaf ik mijn bereidwilligheid aan om een geheimhoudingsovereenkomst te ondertekenen (Annex A). Dat aanbod staat nog steeds. [redacted] staat [redacted] zeer hoog aangeschreven. Hij is bij uitstek in staat om een *peer-review* uit te voeren van ons onderzoek. Daarnaast heeft het RIVM alle benodigdheden in huis om snel een peer-review te kunnen uitvoeren. Ik verwacht dat het RIVM binnen één week een (voorlopige) conclusie kan optekenen van onze data en research paper.

EXTRA MAATREGELEN TER BEPERKING VERSPREIDING SARS-COV-2 EN INFLUENZA

Meerdere specialisten en wetenschappers, waaronder ik, ondersteunen de genomen maatregelen. Hygiëne maatregelen en Social Distancing (1,5m) zijn effectieve maatregelen tegen infectie door direct (mens-tot-mens) contact en respiratoire druppels.

Deze maatregelen zijn echter, vanaf week 44, onvoldoende om een tweede golf te voorkomen. Vanaf week 44 (foutmarge 1 week) daalt de Specifieke Luchtvochtigheid (q) onder de 6 g/kg. Wij verwachten (met 95% zekerheid) dat dit zal leiden tot een exponentiele groei aan COVID-19 gevallen. Daarbij wil ik optekenen dat tijdens de eerste golf, startend in maart, de specifieke luchtvochtigheid (q) al stijgende was. Dit heeft een dempende werking heeft gehad op de eerste golf. Wij concluderen dit op basis van metingen van het KNMI over de jaren 2015 tot heden.

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Als de specifieke luchtvochtigheid in een besloten ruimte verhoogd wordt (naar minimaal 8 g/kg), neemt de vorming van aerosols drastisch af (Annex B). Daarnaast concluderen wij dat het implementeren van ventilatie maar een zeer beperkte effectiviteit biedt. Immers meeste scholen, moderne nieuwgebouwde scholen als uitzondering, hebben nauwelijks ventilatiesystemen, het implementeren is kostbaar en duurt te lang. Daarnaast ondervangen zij van het ontstaan van aerosols niet. En daarmee wordt 50% van de COVID-19 gevallen, in de koudere maanden, niet ondervangen.

Voorsorterend op de resultaten van dit onderzoek, zijn er mogelijke oplossingen, ter bestrijding c.q. voorkoming van COVID-19. In aanvulling op de bestaande maatregelen adviseren wij met spoed:

VERHOGING VAN LUCHTVOCHTIGHEID IN GEZAMENLIJKE RUIMTES

Als onderzoeker wil ik via deze weg mijn enorme bezorgdheid uitspreken. De patronen die we hebben kunnen vaststellen zijn onzes inziens dusdanig verontrustend dat wij gemeend hebben, ondanks het feit dat een *peer-review* nog niet heeft plaatsgevonden onze onderzoeksresultaten toch alvast met u te willen delen. Ter verduidelijking; een *peer-review* kan tot 6 maanden duren.

Ik wil u dan ook met klem verzoeken ons onderzoek op kortst mogelijk termijn aandachtig te bestuderen. U zult ook constateren dat wij ook maar liefst 25 wetenschappelijke studies hebben onderzocht. Velen *peer-reviewed*, die eveneens een verband leggen tussen luchtvochtigheid en de verspreiding van respiratoire virussen. Wij geloven dat het een kwestie van tijd is voordat dit verband "mainstream" wordt aangenomen. Dit brengt echter een groot probleem met zich mee.

Overleg met diverse fabrikanten van luchtbevochtigings- en ventilatie apparatuur hebben ons geleerd dat de vraag naar dergelijke apparatuur nu al fors toeneemt. Dergelijke apparatuur is, tot een vaccin beschikbaar is, de meest effectieve methode om ouderen en mensen met onderliggend lijden te beschermen. Te denk valt aan verpleeghuizen, verzorgingshuizen, etc...

Wij vrezen dat Nederland, net als gebeurde met de mondkapjes, achter het net zal vissen als er niet snel gehandeld wordt. De tijd is te kort en de risico's op sociaaleconomisch gebied te groot om hiermee te wachten. Een tweede golf, met als mogelijk gevolg, een serieuze tweede 'lock-down', zal voor ons allen verstrekkende gevolgen hebben waarvan we de uiteindelijke effecten nog niet kunnen overzien. Wel kan ik u, helaas, voorspellen dat niet handelen zal leiden tot een hoger sterftecijfer. Dit loopt tot in de duizenden.

Vanzelfsprekend ben ik bereid om met u in gesprek hierover te gaan en zaken nader meer gedetailleerd te komen toelichten. In de hoop dat u bovengenoemd onderwerp, na het lezen van mijn brief, even serieus neemt als wij zelf gedaan hebben en in afwachting van uw reactie, verblijven wij,

Hoogachtend,

(10)(2e)
(10)(2e)

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ANNEX A

Gmail (10)(2e) <(10)(2e)@ravelli.net>

RE: Contact en Simulation Data Request

1 message

(10)(2e) <(10)(2e)@rivm.nl> Wed, Mar 18, 2020 at 6:06 PM
To: (10)(2e) <(10)(2e)@ravelli.net>

Beste (10)(2e)

Grappig, ik had (10)(2e) net gesproken. Ik ga naar de mail kijken, en doorzetten bij iemand in de organisatie. We zijn nu redelijk overvoerd, dus het kan even duren voordat je iets terug hoort.

Vriendelijke groeten,

(10)(2e)

From: (10)(2e) <(10)(2e)@ravelli.net>
Sent: woensdag 18 maart 2020 17:59
To: (10)(2e) <(10)(2e)@rivm.nl>
Subject: Fwd: Contact en Simulation Data Request

Geachte Prof.dr. (10)(2e)

(10)(2e) (University of Columbia) heeft mij naar u doorverwezen. Zie zijn reactie hieronder.

Ik stel het zeer op prijs als u onderstaande bericht aan Prof. (10)(2e) zou willen lezen.

Wellicht ten overvloede; Childminders = Gastouders. Deze zijn allen al geografisch door ons gemapped.

Bijvoorbaar hartelijk dank voor uw tijd!

Met vriendelijke groet,

(10)(2e)

---------- Forwarded message ---------
From: (10)(2e) <(10)(2e)@cumc.columbia.edu>
Date: Wed, Mar 18, 2020 at 5:48 PM
Subject: Re: Contact en Simulation Data Request
To: (10)(2e) <(10)(2e)@ravelli.net>, (10)(2e)@columbia.edu <(10)(2e)@columbia.edu>

Dear Mr. (10)(2e)

I don't have the capacity right now to help you. Maybe try (10)(2e) at RIVM— (10)(2e) Dutch and may have access to relevant data for the Netherlands and be using that for country specific simulations.

Stay well,

(10)(2e)

From: (10)(2e) <(10)(2e)@ravelli.net>
Date: Wednesday, March 18, 2020 at 10:19 AM
To: "(10)(2e)@columbia.edu" <(10)(2e)@columbia.edu>
Subject: Contact en Simulation Data Request

Dear Professor (10)(2e)

I am writing to you from the Netherlands. I saw your interview on MSNBC.

Introduction

I represent a Start-Up, founded in 2019, which has developed a platform for childcare.
Following our prime ministers' speech, we came to the conclusion that our platform - with some minor adjustments - can be used to slow down the spread of the virus and at the same time build up controlled group immunity. In addition, using our system can organize childcare for parents with vital functions (doctors, nurses, etc..).

On the one hand, the platform links childcare organizations / childminders vs. on the other, parents with children. In a dynamic way.
For example: The system automatically links parents to nearest childminders, enrollment and logistics.
A match is also made between childminder and child, based on a child profile (including age, allergies, vaccination status and other data).

Our platform contains all the 44,000 registered childcare organizations (including 27,000 childminders) in the Netherlands.
One of the goals of the platform is to better link childminders (maximum 6 children) to parents.

Solution
We believe that childminders can be a vital key in the solution, because of the limitation of the childcare to 6 children and thus limiting exposure.
To better explain the following, I will label parents with their children as a "unit".

The way I like to explain below:
1. In contrast to large childcare locations, childminders are limited to 6 children in The Netherlands. This is a form of social distancing and exposure mitigation.
2. The system can mobilize dynamically and geographically controlled units by accommodating children with a childminder.
3. The dynamics allow the system to allocate periods. So Unit X has now been home for 2 weeks, Unit Y is now working, etc ...
4. In fact, the system can control all units through dynamic planning.
5. In the event of contamination of 1 unit (whether or not detected in parent or child), the planning is immediately adjusted and a quarantine order is sent to all units that are placed with the same childminder and that childminder is also quarantined.
6. After the expiry of the quarantine period, these units and childminders are immune and these childminders can be permanently used for other units.
7. The units in question can return to work and to school (temporarily or otherwise with a childminder).
8. The platform then offers a label "I'm immune, I'm saving lives now" or something similar. This label contains a QR code with the quarantine period.
9. These people - if a full lockdown is set in the future - could still continue to move freely.

Our platform - due to childcare regulations - already contains a complete child profile, including vaccination status, allergies and medical data.
The system also includes a communication module.

If we can access real-time infection (CDC) data, we can use our algorithms in such a way that we avoid ending up in a total lockdown.

In doing so, we partly initiate people going to work again, without ending up in scenario 2 (higher infection rate then can be handled by hospitals).

Naturally, the system can be used in the short term to organize childcare for persons with a vital function.

These parents only need to register on our platform. Our system can already filter for "job titles" to prevent abuse.
The childcare organizations are already in the system.

We believe that deploying this system can save lives as well as help limit financial damage to our economy.

Request

In order to validate our concept, we would like to have access to infection data and infection simulation models. In our opinion, this may be "fake data".
We are only focussed on developing the algorithms so that a proof-of-concept can be made. We want to test our hypothesis.
Of course, a demonstration of the platform can be given.

Can you assist?
I look forward to your response, many thanks.

Sincerely on behalf of our team.

(10)(2e)

Dit bericht kan informatie bevatten die niet voor u is bestemd. Indien u niet de geadresseerde bent of dit bericht abusievelijk aan u is verzonden, wordt u verzocht dat aan de afzender te melden en het bericht te verwijderen. Het RIVM aanvaardt geen aansprakelijkheid voor schade, van welke aard ook, die verband houdt met risico's verbonden aan het elektronisch verzenden van berichten.
www.rivm.nl *De zorg voor morgen* begint vandaag

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ANNEX B

Final: v. 19-08-2020

Environmental risk factors of airborne viral transmission: Humidity, Influenza and SARS-CoV-2 in the Netherlands

(10)(2e) *, (10)(2e) **

Abstract

Objective The relationship between specific humidity and influenza/SARS-CoV-2 in the Netherlands is evaluated over time and at regional level.

Design Parametric and non-parametric correlation coefficients are calculated to quantify the relationship between humidity and influenza, using five years of weekly data. Bayesian spatio-temporal models—with a Poisson and a Gaussian likelihood—are estimated to find the relationship between regional humidity and the daily cases of SARS-CoV-2 in the municipalities and provinces of the Netherlands.

Results An inverse (negative) relationship is observed between specific humidity and the incidence of influenza between 2015 and 2019. The space-time analysis indicates that an increase of specific humidity of one gram of water vapor per kilogram of air (1 g/kg) is related to a reduction of approximately 5% in the risk of COVID-19 infections.

Conclusions The increase in humidity during the outbreak of the SARS-CoV-2 in the Netherlands helped to reduce the risk of regional COVID-19 infections. Public policies that promote higher levels of specific humidification—above 6 g/Kg—can lead to significant reductions in the spread of respiratory viruses, such as influenza and SARS-CoV-2.

* Contact: (10)(2e) @ravelli.net. LinkedIn: (10)(2e)
** University of Agder (Norway). ORCID: https://orcid.org/0000-0001-5401-780X

1. Introduction

Previous experimental evidence indicates that that the aerosolization of secretions lubricating the vocal cords can be a major source of microscopic droplet (microdroplet) virus infections (Morawska et al., 2009). Evidence of airborne spread of the severe acute respiratory syndrome virus (SARS) is provided by Yu et al. (2004). Recent studies also suggest the possibility of airborne transmission of SARS-CoV-2 through respiratory air droplets and aerosols (Morawska & Cao, 2020; Liu et al., 2020).

Weather factors—such as humidity and temperature—are suspected of playing a role in the transmission of viral particles through aerosolized droplet nuclei or aerosols. Shaman & Kohn (2009) argue that the differences in humidity provide an explanation for the observed variability of influenza and its transmission. Weather conditions can have a similar effect on SARS-CoV-2 (COVID-19), as Ijaz et al. (1985) find that airborne inactivation of the human coronavirus 229E is affected by temperature and relative humidity, while Casanova et al. (2010) show in an experimental setting that both temperature and absolute humidity affect the environmental survival of surrogates of mammalian coronaviruses.

Based on observational data, the relationship between SARS-CoV-2 and weather has been recently analyzed by Bukhari & Jameel (2020), Gupta et al. (2020), Oliveiros et al. (2020), Sajadi et al. (2020) and Ma et al. (2020). These studies find a negative correlation between absolute humidity and the spread of SARS-CoV-2, indicating that low levels of humidity increase the risk of COVID-19 cases. Sajadi et al. (2020), for example, investigate weather conditions worldwide and conclude that the community transmission of SARS-CoV-2 is consistent with average temperatures of 5° to 11°C, combined with low specific humidity between 3 to 6 g/kg.

Our study provides new evidence about the relationship between specific humidity and the risk of influenza and COVID-19 cases. Five years of hourly weather data from 34 regional weather stations in the Netherlands is analyzed against five years of weekly data of influenza cases, as well as daily regional data of COVID-19 cases, hospitalizations, and deaths. The Netherlands has accurate and easily accessible data that allows for a precise estimation of the relationship between weather conditions and the spread of viral diseases.

In our study, parametric and non-parametric correlations are calculated for specific humidity and influenza/SARS-CoV-2 at country-level. An inverse (negative) relationship is observed between specific humidity and the incidence of influenza between 2015 and 2019, but a positive correlation is found between specific humidity and the reported cases of COVID-19. Since the positive correlation between specific humidity and COVID-19 may be caused by the use of aggregated data at national level—besides the lack of herd immunity—a Bayesian spatio-temporal disease model

for the Netherlands is estimated at municipality and province level. This model allows to quantify the relation of COVID-19 cases with the specific humidity in the Netherlands at regional sub-national levels and over time.

The results of the spatio-temporal disease model indicate that the increase of specific humidity during the outbreak of the SARS-CoV-2 helped to reduce the risk of regional COVID-19 cases in the Netherlands. Specifically, an increase of specific humidity of one gram of water vapor per kilogram of air (1 g/kg) is related to a reduction of approximately 5% in the risk of COVID-19 cases.

2. Data

Weekly data of influenza reports were collected for the years 2015 to 2019 from the Nivel Primary Care Database (Nivel Zorgregistraties Eerste Lijn). Daily COVID-19 data (Reported Infections, Hospitalizations and Mortality) was provided by The Dutch National Institute for Public Health and the Environment (RIVM). RIVM is the government agency focused as Centre for Infectious Disease Control (CDC), under supervision of the Dutch Government. The COVID-19 data covers the twelve provinces and the 355 municipalities in the Netherlands, from March 13th to July 9th.

Specific humidity (q) was calculated with the data from 34 weather stations, spread across The Netherlands. This data was provided by The Royal Netherlands Meteorological Institute (KNMI), the Dutch national weather service. Since KNMI only reports relative humidity (h), specific humidity q was calculated using the Rotronic formula[1], which is based on the UK National Physical Laboratory guide for the measurement of humidity (National Physical Laboratory, 1996):

$$q = \xi \frac{h d_w}{(d_m - d_w)} \quad (1)$$

In (1), q is specific humidity of air vapor mixture (expressed in g/Kg), h is relative humidity (in percentage), d_w is the density of water vapor (kg/m^3), d_m is density of the moist or humid air (kg/m^3) and $\xi = .622$. Specific humidity is analyzed instead of relative humidity because relative humidity is affected by the surrounding temperature. Specific humidity in contrast remains the same in indoor and outdoor conditions[2]. The hourly weather data provided by the KNMI was aggregated at daily and weekly levels using the average values during the time periods.

[1] The Rotronic technical note about humidity definitions is freely available at: 0https://www.rotronic.com/media/productattachments/files/h/u/humidity_definitions_weba.pdf?_ga=2.192612136.342104324.1597340506-398495933.1597340506

[2] For example, weather stations may report a temperature of 5°C and a relative humidity of 35% for the outside environment (equal to a specific humidity of 1.87g/kg). However, inside the households, the temperature can be 21°C with a relative humidity of 12% due to heating systems, but specific humidity will remains the same (1.87g/kg) regardless of the temperature.

Additional population data was used in the spatial-time models to calculate the incidence of SARS-CoV-2 at intra-regional level. This data was provided by the national statistical office, Statistics Netherlands (CBS) and is also used by the RIVM.

3. Methods

Parametric and non-parametric correlation coefficients were calculated between specific humidity q and the incidence of influenza and SARS-CoV-2. Spatio-temporal disease models were estimated with the daily data of specific humidity (q_{it}) and SARS-CoV-2 (y_{it}) in the Netherlands.

In the space-time analysis, the Besag-York-Mollié (BYM) spatio-temporal model (Besag et al., 1991) was used to estimate the impact of specific humidity on the risk of SARS-CoV-2 (COVID-19) cases at province and municipality level. In the BYM model, the number of SARS-CoV-2 cases follows a Poisson stochastic process for each area i and time points t, $y_{it} \sim \mathcal{P}(\lambda_{it})$. The parameter λ_{it} is defined by the ecological regression:

$$\begin{cases} \lambda_{it} = E_{it} p_{it} \\ p_{it} = \exp\left(\alpha + v_i + u_i + (\beta_t + \tau_i)t + \beta_q q_{it}\right) \end{cases} \quad (2)$$

where E_{it} is the expected number of cases in each area, at each point in time, p_{it} is the ratio between the number of observed cases y_{it} and the number of expected cases, α is the average rate of cases in all the areas, v_i is the unstructured area-specific effect, which follows a Gaussian prior $v_i \sim \mathcal{N}(0, \sigma_v^2)$, and u_i is the spatially structured area-specific effect, modelled with an intrinsic conditional autoregressive prior that takes into account the number of j-areas which share boundaries with the i-areas ($j \neq i$), i.e. the neighbors of each province/municipality. See Blangiardo & Cameletti (2015, pp. 178-179) for details.

In (2), the temporal component t is modelled following the parametric approach of Bernardinelli et al. (1995), where β_t represents the global time effect, and $\tau_i \sim \mathcal{N}(0, 1/\sigma_\tau^2)$ is the differential trend that captures the interaction between time and space. Specific humidity levels (q_{it}) were included as a risk factor in the spatio-temporal model (1) to evaluate their impact on the risk of SARS-CoV-2 cases, measured by the parameter β_q. When the incidence of SARS-CoV-2 per 100,000 population is used as the dependent variable, a Gaussian likelihood is used instead of the Poisson model in equation (2).

4. Results

Figure 1 shows the weekly historical patterns of specific humidity q and the incidence of influenza in the Netherlands, from 2015 to 2019. Specific humidity q during the winter periods is between 3 and 6 g/kg, while in the summer specific humidity is above 8 g/kg. The highest incidence of influenza infection is observed in weeks with a specific humidity of less than 6 g/kg. Particularly, a higher incidence is observed in children of less than 4 years and individuals with 65 years or more (Figure 2a). Above 6 g/kg, a significant drop in infections is observed. The opposite is also true: the rate of influenza cases is 5.91 higher when specific humidity levels are approximately 2 g/kg compared to the average cases at 8 g/kg (Table 1).

Table 1. Average incidence of influenza cases at different intervals of specific humidity

Specific humidity	Average incidence of influenza per 100000 people
Below 2 g/kg	147.3
Between 2 and 3	135.4
Between 3 and 4	110.9
Between 4 and 5	79.7
Between 5 and 6	54.4
Between 6 and 7	33.2
Between 7 and 8	29.5
Between 8 and 9	24.9
Between 9 and 10	17.2
Above 10	15.8

Figure 2b illustrates the inverse non-linear relationship between the levels of specific humidity and the weekly incidence of influenza. The ordinary Pearson correlation of specific humidity with influenza cases is negative and equal to –.6986 (t-value: –15.713, p-value: 0.0000). The value of the non-parametric Spearman correlation is equal to –0.8083 (t-statistic: –22.0993, p-value: 0.0000).

In the case of SARS-CoV-2, there is a positive correlation between humidity levels and the daily COVID-19 cases in the Netherlands (Figure 3). The Pearson correlation is equal to .7016 (t-value: 10.651, p-value: 0.0000), and the Spearman correlation is 0.8389 (t-statistic: 16.6734, p-value: 0.0000). This positive correlation can be explained by the lack of herd immunity—due to the novelty of the SARS-CoV-2—, the increasing number of tests, and the use of aggregate data at country level which does not capture the dissimilarities of specific humidity at sub-national levels in the Netherlands.

Figure 1. Specific humidity and incidence of influenza in the Netherlands Weekly historical observations per year

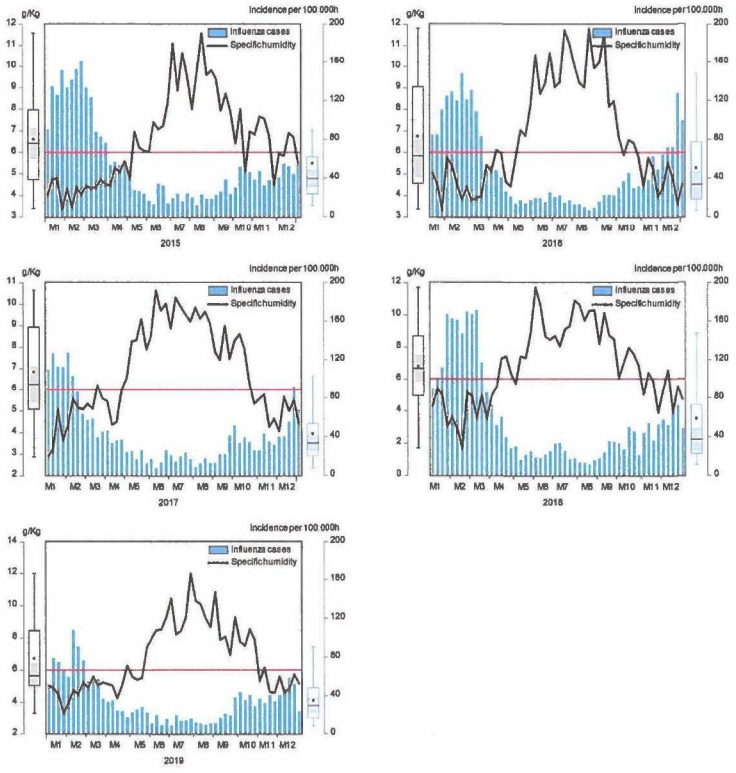


Figure 2. Specific humidity and incidence of influenza for age categories in the Netherlands.
a: Weekly historical observations (left), b: bivariate scatterplot (right)

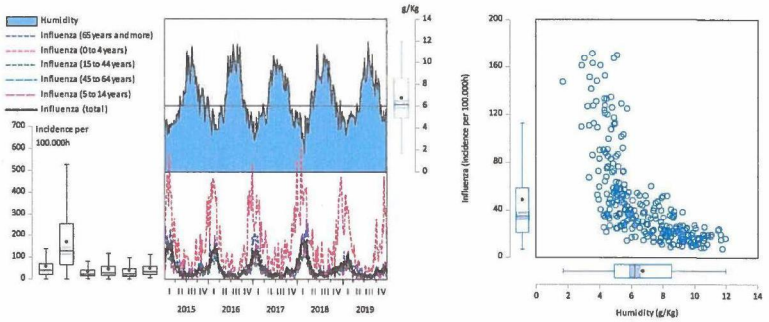
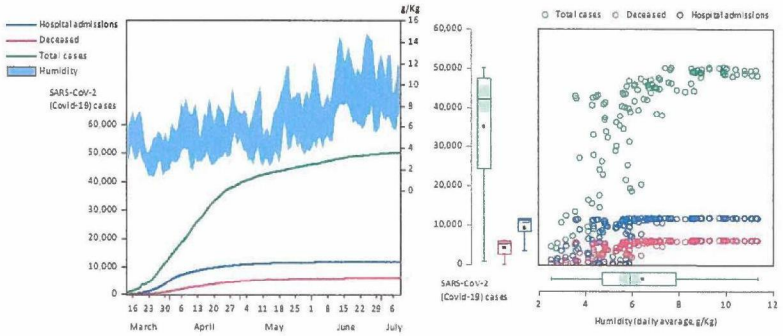


Figure 3. Specific humidity and SARS-CoV-2 (Covid-19) cases in the Netherlands
a: Daily historical observations (left), b: bivariate scatterplot (right)



In order to take into account the differential spatial and temporal patterns of specific humidity across the Netherlands during the outbreak of the COVID-19, a Bayesian spatial-time model based on a Poisson stochastics process was estimated for the number of reported cases of SARS-CoV-2, at municipality and province level. The increase in testing, which increases reported COVID-19 cases, was controlled by

relativizing the number of COVID-19 cases with the population at municipality and province level, i.e. estimating an additional Gaussian space-time model for the incidence of COVID-19 cases per 100,000 people[3].

Table 2 shows the results of estimating the fixed-effects $\{\alpha, \beta_t, \beta_q\}$ of the spatio-temporal model. The low standard deviation of the posterior means in all the models indicates a good level of the accuracy of integrated nested Laplace approximation in the approximate Bayesian inference. The value of the exponentiated estimate of β_t implies a 1.5% daily rate of infection of SARS-CoV-2 in the Netherlands from March to July of 2020, with a 95% credibility interval ranging from 1.47% to 1.62%. The negative sign of the mean estimate of β_q—as well as the sign of the low and upper limit of the 95% credible interval—suggests that regions with higher specific humidity levels have, on average, lower number of COVID-19 cases in the Netherlands. Specifically, the estimated values of $\hat{\beta}_q = -0.048$ at province level and $\hat{\beta}_q = -0.053$ at municipality level in the Poisson space-time model indicate that an increase of one gram of water vapor per kilogram of air (1 g/kg) is related to a reduction of around 5% in the risk of Covid-19 cases.

Table 2. Estimation results: Besag-York-Mollie spatio-temporal disease model of daily (t) COVID-19 cases and specific humidity (q) in the Netherlands

	Parameter	Area's break	Mean estimate	Standard deviation	Credible interval	
					2.5%	97.5%
Number of cases of SARS-CoV-2 (COVID-19)	α	Province	6.770375	0.092920	6.585284	6.955255
		Municipality	3.407532	0.043961	3.321127	3.493834
	β_t	Province	0.015331	0.000354	0.014625	0.016037
		Municipality	0.015307	0.000035	0.015238	0.015375
	β_q	Province	-0.047696	0.000361	-0.048404	-0.046988
		Municipality	-0.053141	0.000364	-0.053855	-0.052427
Incidence of cases of SARS-CoV-2 (COVID-19) per 100,000h	α	Province	67.440261	2.982071	61.584535	73.291041
		Municipality	87.629212	3.374872	81.003201	94.249693
	β_t	Province	2.448832	0.049035	2.352544	2.545038
		Municipality	2.866350	0.013162	2.840509	2.892170
	β_q	Province	-6.231110	0.706851	-7.619118	-4.844281
		Municipality	-8.399374	0.194467	-8.781178	-8.017889

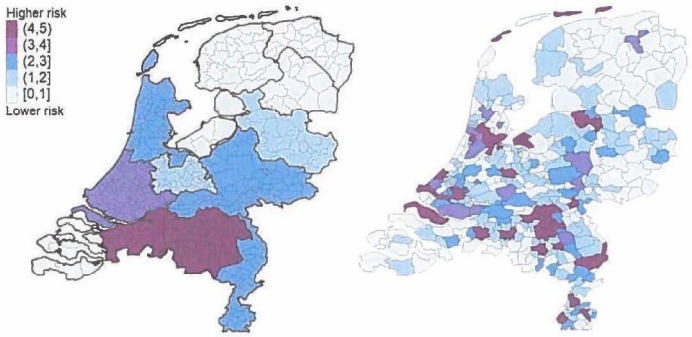
[3] The Netherlands increased COVID-19 testing from 55,000 weekly tests in March to 110,000 tests per week in July 2020. The testing was only focused on care workers in March, but now the entire population is subject to testing. Due to the possible bias caused by testing, space-time models were also estimated using data of the number of hospitalizations, and similar results were obtained as those for reported cases. The results for hospitalization are available upon request.

Similar results are obtained using a Gaussian space-time model for the incidence of SARS-CoV-2 cases per 100,000 population in the Netherlands. On average, regions with higher levels of specific humidity showed a lower incidence of COVID-19 cases per 100,000 people, on a magnitude of $\hat{\beta}_q = -6.23$ at province level and $\hat{\beta}_q = -8.4$ at municipality level.

Figure 4 shows the area-specific relative risks of COVID-19 in the Netherlands—at province and municipality level—calculated with the random-effects $\vartheta = \exp(v_i + u_i)$ estimated with the spatio-temporal models. The regions located in the North of the country, where specific humidity tends to be higher, show a lower risk of COVID-19 cases. In contrast the regions with less specific humidity, in the South East of the country, display higher levels of relative risk of SARS-CoV-2 cases.

Interestingly, municipalities with the highest concentration of conservative orthodox Calvinist Protestants in the country, i.e. those in the 'Bible belt', have a higher risk of SARS-CoV-2, compared to other regions in the Netherlands. The identification of this type of regions with a high risk of COVID-19 cases can help to allocate resources during the COVID-19 pandemic (Cordes and Castro, 2020).

Figure 4. Area-specific relative risk* of SARS-CoV-2 in the Netherlands



(*) Relative risk: residual risk after regional specific humidity (q) levels are taken into account.
Area's break: province level (left) and municipality level (right).

5. Discussion

Higher levels of specific humidity (q) were found to be related to a lower number of reported cases of respiratory viruses in the Netherlands. An inverse non-linear relationship between specific humidity and influenza is observed historically between 2015 and 2019. A similar inverse (negative) relationship between specific humidity and SARS-Cov-2 cases is found using spatio-temporal models that consider the differential patterns of specific humidity (q) and SARS-Cov-2 cases at municipality and province levels in the Netherlands.

The results are in line with those of Yu et al. (2004), Morawska et al. (2009), Shaman & Kohn (2009), Morawska & Cao (2020), Liu et al. (2020), Sajadi et al (2020), Gupta et al. (2020) and Ma et al. (2020). The findings are consistent with the hypothesis that suggests that SARS-CoV-2 spreads through airborne aerosolization, since lower levels of specific humidity q lead to a higher concentration of aerosols when a dry air increases the evaporation of respiratory droplets, i.e. when droplets smaller in diameter than a few micrometers—usually referred to as "droplet nuclei"—evaporate to about half their initial size (Brienen et al., 2010). In the case of influenza, for example, Teunis et al. (2010) shows that the probabilities of exposure and infection risk of aerosol and droplet transmission are within the same order of magnitude, but intranasal inoculation leads to about 20 times lower infectivity that when the virus is delivered in an inhalable aerosol.

In practice, the findings suggest that public policies that promote higher levels of specific humidification—above 6 g/Kg—can lead to significant reductions in the spread of respiratory viruses, such as influenza and SARS-CoV-2. For example, the deployment of hygrometers aimed at measuring specific humidity can guide the public behavior in the face of a warning of an increased risk of infection[4]. The results also imply that the use of air conditioning (which decreases the specific humidity in a cooled area), must be complemented with humidification during the fall and winter periods, particularly when specific humidity q decreases below 6 g/kg.

Future studies can study the interaction effects of sunlight with humidity, as sunlight radiation may act as and additional environmental factor in the reduction and prevention of the risk of SARS-CoV-2 (see Rosario et al., 2020), since solar radiation plays an important role in vitamin D production, which seems to play a role in reducing COVID-19 infections (Grant et al., 2020; Whittemore, 2020).

[4] For example, smart social distancing regulations may take into account local humidity levels, per municipality, and allow social gatherings in outside spaces (as e.g. terraces) on humid days. At the same, social gatherings on cloudy and cold days with low humidity, or in dry environments (such as restaurants), may be discouraged, unless these environments have approved humidification solutions implemented. If increased humidification is not possible, air purification with HEPA filters and ionization can be alternative solutions to deactivate viral aerosols.

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References

Bernardinelli, L., Clayton, D., Pascutto, C., Montomoli, C., Ghislandi, M., & Songini, M. (1995). Bayesian analysis of space-time variation in disease risk. Statistics in medicine, 14(21-22), 2433-2443.

Besag, J., York, J., & Mollié, A. (1991). Bayesian image restoration, with two applications in spatial statistics. Annals of the institute of statistical mathematics, 43(1), 1-20.

Blangiardo, M., & Cameletti, M. (2015). Spatial and spatio-temporal Bayesian models with R-INLA. John Wiley & Sons.

Brienen, N. C., (10)(2e)., Wallinga, J., Van Steenbergen, J. E., & Teunis, P. F. (2010). The effect of mask use on the spread of influenza during a pandemic. Risk Analysis: An International Journal, 30(8), 1210-1218.

Bukhari, Q., & Jameel, Y. (2020). Will coronavirus pandemic diminish by summer? Available at SSRN 3556998.

Casanova, L. M., Jeon, S., Rutala, W. A., Weber, D. J., & Sobsey, M. D. (2010). Effects of air temperature and relative humidity on coronavirus survival on surfaces. Applied and environmental microbiology, 76(9), 2712-2717.

Cordes, J., & Castro, M. C. (2020). Spatial analysis of COVID-19 clusters and contextual factors in New York City. Spatial and Spatio-temporal Epidemiology, 100355.

Fineberg, H. V., & National Research Council. (2020). Rapid expert consultation on the possibility of bioaerosol spread of SARS-CoV-2 for the COVID-19 pandemic (April 1, 2020). In The National Academies Press NRC. The National Academies Press, National Research Council, Washington, DC.

Grant, W. B., Lahore, H., McDonnell, S. L., Baggerly, C. A., French, C. B., Aliano, J. L., & Bhattoa, H. P. (2020). Evidence that vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths. Nutrients, 12(4), 988.

Gupta, S., Raghuwanshi, G. S., & Chanda, A. (2020). Effect of weather on COVID-19 spread in the US: a prediction model for India in 2020. Science of The Total Environment, 138860.

Ijaz, M. K., Brunner, A. H., Sattar, S. A., Nair, R. C., & Johnson-Lussenburg, C. M. (1985). Survival characteristics of airborne human coronavirus 229E. Journal of General Virology, 66(12), 2743-2748.

Kim, S., & Castro, M. C. (2020). Spatiotemporal pattern of COVID-19 and government response in South Korea (as of May 31, 2020). International Journal of Infectious Diseases.

(10)(2e)., Ning, Z., Chen, Y., Guo, M., (10)(2e)., Gali, N. K., ... & Liu, X. (2020). Aerodynamic characteristics and RNA concentration of SARS-CoV-2 aerosol in Wuhan hospitals during COVID-19 outbreak. BioRxiv.

Ma, Y., Zhao, Y., Liu, J., He, X., Wang, B., Fu, S., & Luo, B. (2020). Effects of temperature variation and humidity on the death of COVID-19 in Wuhan, China. Science of The Total Environment, 138226.

Morawska, L. J. G. R., Johnson, G. R., Ristovski, Z. D., Hargreaves, M., Mengersen, K., Corbett, S., ... & Katoshevski, D. (2009). Size distribution and sites of origin of droplets expelled from the human respiratory tract during expiratory activities. Journal of Aerosol Science, 40(3), 256-269.

Morawska, L., & Cao, J. (2020). Airborne transmission of SARS-CoV-2: The world should face the reality. Environment International, 105730.

National Physical Laboratory (1996). A Guide to the Measurement of Humidity. The Institute of Measurement and Control, United Kingdom. https://rotronic.com/media/productattachments/files/n/p/npl_guide_to_humidity.pdf

Oliveiros, B., Caramelo, L., Ferreira, N. C., & Caramelo, F. (2020). Role of temperature and humidity in the modulation of the doubling time of COVID-19 cases. medRxiv.

Rosario, D. K., Mutz, Y. S., Bernardes, P. C., & Conte-Junior, C. A. (2020). Relationship between COVID-19 and weather: Case study in a tropical country. International Journal of Hygiene and Environmental Health, 113587.

Sajadi, M. M., Habibzadeh, P., Vintzileos, A., Shokouhi, S., Miralles-Wilhelm, F., & Amoroso, A. (2020). Temperature and latitude analysis to predict potential spread and seasonality for COVID-19. Available at SSRN 3550308.

Shaman, J., & Kohn, M. (2009). Absolute humidity modulates influenza survival, transmission, and seasonality. Proceedings of the National Academy of Sciences, 106(9), 3243-3248.

Teunis, P. F., Brienen, N., & Kretzschmar, M. E. (2010). High infectivity and pathogenicity of influenza A virus via aerosol and droplet transmission. Epidemics, 2(4), 215-222.

Whittemore, P. B. (2020). COVID-19 fatalities, latitude, sunlight, and vitamin D. American Journal of Infection Control.

Yu, I. T., Li, Y., Wong, T. W., Tam, W., Chan, A. T., Lee, J. H., ... & Ho, T. (2004). Evidence of airborne transmission of the severe acute respiratory syndrome virus. New England Journal of Medicine, 350(17), (10)(2e).

ANNEX C

Epidemics 2 (2010) 215–222

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High infectivity and pathogenicity of influenza A virus via aerosol and droplet transmission

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ABSTRACT

Influenza virus may be transmitted through the respiratory route by inhalation of an aerosol of non-sedimenting droplets, or by deposition of sedimenting droplets in the upper respiratory tract. Whichever of these is the predominant route for infection with influenza virus has been subject of continuing debate, resulting in detailed studies of aerosol versus droplet exposure. A decisive knowledge gap preventing a satisfying conclusion is absence of a well defined human dose response model for influenza virus.

This study uses a hierarchical approach generalizing over twelve human challenge studies collected in a literature search. Distinction is made between aerosol and intranasal inoculation. The results indicate high infectivity via either route, but intranasal inoculation leads to about 20 times lower infectivity than when the virus is delivered in an inhalable aerosol.

A scenario study characterizing exposure to airborne virus near a coughing infected person in a room with little ventilation demonstrates that with these dose response models the probabilities of infection by either aerosol or sedimenting droplets are approximately equal. Droplet transmission results in a slightly higher illness risk due to the higher doses involved.

Establishing a dose response model for influenza provides a firm basis for studies of interventions reducing exposure to different classes of infectious particles. More studies are needed to clarify the role of different modes of transmission in other settings.

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Introduction

Transmission of influenza is thought to occur through contact with small infectious particles. Infectious virus present in or on the mucosae of the upper respiratory tract is expelled through coughing or sneezing, or even through normal exhalation, producing small droplets that may contain various amounts of virus (Fabian et al., 2008; Blachere et al., 2009). Droplets that are small enough may evaporate rapidly, leaving a microscopic particle that can remain suspended in air for an indefinite time (Riley, 1974). While part of the produced infectious particles may be small enough for a non-sedimenting aerosol, the remainder of the expelled droplets is bigger and tends to be removed from the air by sedimentation (Duguid, 1946). Virus present on surfaces (skin or inanimate) may be transferred to mucosa by hand and still cause infection (Ryan et al., 2001). Virus may thus infect by different routes. The relative importance of these routes for transmission has been debated intensively but it still remains unclear if any route is dominant (Tellier, 2006; Weber and Stilianakis, 2008).

The different modes of transmission of respiratory infections may be studied by quantitative modelling of production of droplets containing virus and their transport to mucosal surfaces in a susceptible host (Xie et al., 2007; Atkinson and Wein, 2008; Nicas and Jones, 2009). Although such studies describe exposure to respiratory virus with considerable sophistication, one essential stage in the infection chain, the dose response relation for infection, has remained relatively obscure. Infectivity estimates are based on small data sets containing few observations and biological variation (heterogeneity) in infectivity is ignored.

The present paper attempts to fill this gap by using a hierarchical approach to dose response modelling, based on data from several human challenge studies reported in scientific journals. This allows us to provide a quantitative description of the infectivity of influenza A virus in humans, either by aerosol inoculation or by intranasal droplet inoculation, including its heterogeneity among hosts and virus isolates. Based on these dose response models, improved estimates of the risk of infection (and of acute respiratory symptoms) can be

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Table 1
Wild-type influenza virus challenge studies with aerosol inoculation.

Reference	Virus type	Dose ($TCID_{50}$)	Exposed	Infected	Ill
Henle et al. (1946)	A (F-12)	0.6×10^{10}[a]	4	—[b]	4
		0.6×10^{10}[a]	4	—[b]	4
		0.6×10^{9}[a]	4	—[b]	1
		0.6×10^{8}[a]	4	—[b]	1
	A (F-99)	$0.6\times10^{8.5}$[a]	6	—[b]	5
		$0.6\times10^{8.5}$[a]	4	—[b]	4
		$0.6\times10^{7.5}$[a]	6	—[b]	2
	A (PR-8)	$0.6\times10^{8.2}$[a]	33	—[b]	27
Jao et al. (1965)	A2 (Elisberg)	30	30	—[c]	12
Alford et al. (1966)	A2/Bethesda/10/63	126	3	0	0[d]
		78	3	0	0[d]
		59	3	1	0
		1	1	1	1
		2	4	1	0
		5	9	4	3

[a] Not tissue culture but ID_{50} in chick embryos.
[b] Not studied.
[c] Virus excretion and seroconversion studied but not reported.
[d] These subjects were presumably immune, as they had high antibody levels to the virus.

Table 2
Wild-type influenza virus challenge studies with nasal inoculation.

Reference	Virus type	Dose ($TCID_{50}$)	Exposed	Infected	Ill
Henle et al. (1946)	A (F-12)	$10^{10.0}$[a]	4	—[b]	1
	A (F-99)	$10^{8.5}$[a]	6	—[b]	0
Murphy et al. (1973)	A/Bethesda/88 (H3N2)	$10^{4.5}$	7	7	7[c]
Murphy et al. (1980)	A/Hong Kong/77 (H1N1)	$10^{4.2}$	6	6	5
	A/Udorn/72 (H3N2)	$10^{4.0}$	6	5	5
	A/Alaska/77 (H3N2)	$10^{4.2}$	8	8	4
Clements et al. (1983)	A/Alaska/6/77 (H3N2)	$10^{4.2}$	8	8	4
Clements et al. (1984b)	A/Washington/897/80 (H3N2)	$10^{6.0}$	24	23	11
Clements et al. (1984a)	A/Washington/897/80 (H3N2)[d]	$10^{6.0}$	24	23	11
Murphy et al. (1984)	A/California/10/78 (H1N1)	$10^{4.0}$	9	9	5
Murphy et al. (1985)	A/Washington/897/80 (H3N2)[d]	$10^{6.0}$	24	23	11
Clements et al. (1986)	A/Washington/897/80 (H3N2)[d]	$10^{6.0}$	24	23	11
Snyder et al. (1986)	A/California/10/78 (H1N1)	$10^{4.5}$	14	13	6
	A/Korea/1/82 (H3N2)	$10^{6.2}$	14	14	7
Sears et al. (1988)	A/Texas/1/85 (H1N1)	$10^{6.4}$	28	26	12
	A/Bethesda/1/85 (H3N2)	$10^{7.0}$	10	10	3
Youngner et al. (1994)	A/Kawasaki/9/86 (H1N1)	$10^{7.0}$	14	14	6

[a] Not tissue culture but ID_{50} in chick embryos.
[b] Not studied.
[c] Of these subjects, 6 had severe symptoms with fever, 1 had mild symptoms without fever.
[d] Same as Clements et al. (1984b).

calculated for aerosol and for droplet transmission. For a given exposure scenario the relative strengths of either transmission mode can then be estimated.

The improved dose response information contributes to quantitative estimates of the infectious droplet transmission process by including variation in host susceptibility as well as variation in infectivity among different virus isolates.

Dose response assessment

A literature study of human challenge experiments with influenza virus has produced two sets of studies, with virus delivered either via aerosol inhalation or via intranasal droplet inoculation. Aerosol inoculation may allow the virus to reach smaller bronchiae where receptor densities are high (Hatch, 1961) and infection may be more likely. Alternatively, deposition of a small droplet of virus suspension onto the nasal mucosa may serve as a model for transmission via droplets of sedimenting sizes (Brankston et al., 2007).

To analyze these dose response data, a hierarchical model is used, extending the hit theory model for microbial infection (Haas, 1983; Teunis and Havelaar, 2000) to a multilevel framework (Teunis et al., 2008b).

Dose response model

When exposed to a sample taken from a well mixed microbial suspension the probability of exposure to one or more infectious virus particles is

$$\mathrm{Prob}_{\exp}(cV) = 1-e^{-cV} \tag{1}$$

assuming a volume V was inoculated from a suspension of Poisson distributed particles with concentration c.

In case each particle is equally infectious, the dose response relation for infection is (Riley and O'Grady, 1961)

$$\mathrm{Prob}_{\mathrm{inf}}(cV|p_m) = 1-e^{-p_m cV} \tag{2}$$

where any infectious virus survives the host barriers to infection with probability p_m (Teunis and Havelaar, 2000). Biological variation in host susceptibility and virus infectivity may be expressed as (random) variation in p_m. The resulting (marginal) dose response model

$$\mathrm{Prob}_{\mathrm{inf}}(cV|\alpha,\beta) = 1-{}_1F_1(\alpha,\alpha+\beta;-cV) \tag{3}$$

where ${}_1F_1$ is a (Kummer) confluent hypergeometric function and α and β the parameters of a beta distribution describing the variation in p_m, is the beta-Poisson model for microbial infection (Haas, 1983; Teunis and Havelaar, 2000).

A person infected with influenza virus may develop symptoms of acute respiratory illness with probability again depending on the inoculated dose. A conditional dose response model for illness in infected subjects is defined as

$$\mathrm{Prob}_{\mathrm{ill}|\mathrm{inf}}(cV|\eta,r) = 1-(1+\eta cV)^{-r} \tag{4}$$

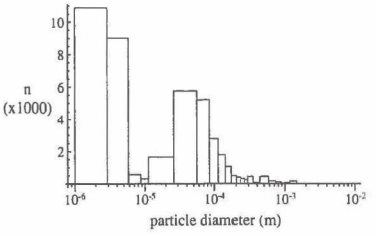

Fig. 1. Counts of particles of various diameters in air expelled by (90) coughs (Loudon and Roberts, 1967).

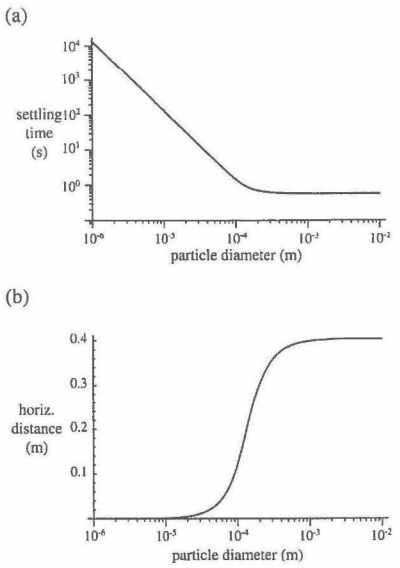

Fig. 2. (a) Average settling time (in s) for a particle produced at body height (1.6 m) to reach the floor, as a function of particle diameter. (b) Horizontal distance (in m) travelled when a particle is expelled with velocity 1 m/s and falls 0.8 m (half body height).

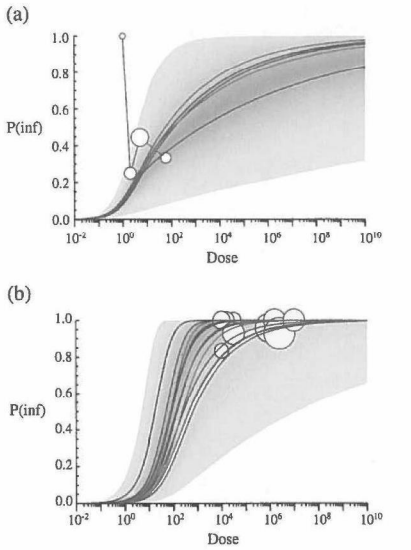

Fig. 4. Dose response for infection by wild type influenza A virus, via aerosol or intranasal droplet inoculation. 'Best fit' dose response relations and density graph of predicted infection risk as a function of dose (margins span 99% interval). Also shown is a bubble chart of observed fractions (symbol size proportional to numbers exposed).

assuming a hazard function of developing symptoms that depends on the duration of infection (parameters η and r describe a (gamma) distribution for the dose dependent duration of infection). Details can be found in Teunis et al. (1999).

As subject status is binary (infected or not, symptomatic or not) the model may be analyzed with a binomial likelihood function (Teunis and Havelaar, 2000) that can be extended to a two-level framework (Teunis et al., 2002, 2008b). Additional information on statistical analysis is provided in an online appendix (supporting information).

Dose response data

Three studies administered the virus through inhalation of a standardized aerosol of influenza A virus isolated from patients (5 different isolates, shown in Table 1). Twelve papers reported on influenza A virus challenge through intranasal droplet inoculation, three of which appeared to re-report results from an earlier study, leaving nine studies with 14 different isolates (Table 2). Note that the oldest study (Henle et al., 1946) only documented illness responses: numbers of infected subjects (excreting virus) were not reported. Because illness is conditional on infection these data still provide information about the infectivity of the virus.

In most studies the virus dose was expressed in $TCID_{50}$ units. This is the median 50% tissue culture infectious dose ($TCID_{50}$). Assuming perfect susceptibility 1 $TCID_{50}$ would correspond to $log2 \approx 0.69$ infectious virus particles because the dose response for a perfectly susceptible host system is $P_{inf}(D) = 1 - e^{-D}$, hence $1 - e^{-TCID_{50}} = 0.5$. This is quite close to 1 and therefore we feel safe in assuming that 1 $TCID_{50}$ approximately equals 1 infectious virus particle (Blachere et al., 2009). In one of the studies the dose was expressed as 50% infectious dose in chick embryo culture (Henle et al., 1946). Chick embryos are also a highly sensitive medium (Hirst, 1942) and it does not seem very likely that the chick embryo assay is less susceptible than the tissue culture assay by more than an order of magnitude (Donald and Isaacs, 1954). Therefore, in the following analysis it is assumed that 1 $EID_{50} = 1$ $TCID_{50} = 1$ virus particle.

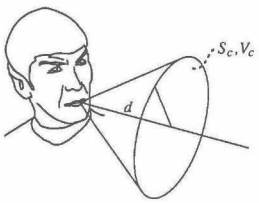

Fig. 3. Conical region where sedimenting droplets (>10 μm) may occur after expulsion through coughing or sneezing. The horizontal distance d (and the circular area S_c and the corresponding volume V_c) depends on the initial velocity and the particle size.

Exposure

Droplets are generated during breathing, coughing or sneezing as expelled air strikes surfaces covered with mucus in the upper respiratory tract. Various accounts have been published of the diameters of the fluid particles produced during either of these activities, with

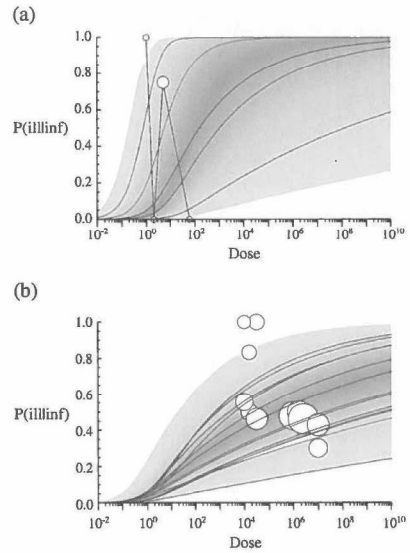

Fig. 5. Dose response for illness given infection by wild type influenza A virus, via aerosol or intranasal droplet inoculation. 'Best fit' dose response relations and density graph of predicted conditional illness risk as a function of dose. Also shown is a bubble chart of observed fractions (symbol size proportional to numbers infected).

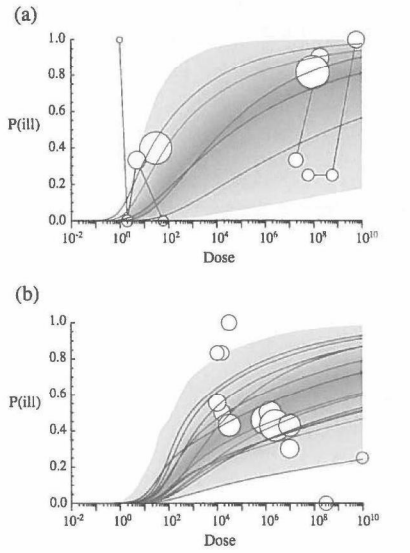

Fig. 6. Dose response for illness by wild type influenza A virus, via aerosol or intranasal droplet inoculation. 'Best fit' dose response relations and density graph of predicted illness risk as a function of dose. Also shown is a bubble chart of observed fractions (symbol size proportional to numbers exposed).

comparable outcomes (Duguid, 1946; Loudon and Roberts, 1967; Xie et al., 2009). A review of airborne infectious particle emission (Nicas et al., 2005) describes three different studies reporting particle size distributions. In order to not unduly complicate the following account of airborne exposure the sizes recorded in one study (Loudon and Roberts, 1967) will be used, because that study provides a detailed account of the particle size distribution, combining small non-sedimenting particles and large size particles that sediment rapidly. The reported particle diameters range from 1 μm to more than 1.5 mm, and the frequencies counted in air expelled with 90 coughs are given.

There appears to be a bimodal distribution of small and large particles (Fig. 1) and a binary mixture of lognormal distributions provides a good fit of these observed particle sizes. Small particles have a mean size of 3.0 μm (99% range 1.27–6.25 μm). The average diameter of large particles is 111.4 μm (99% range 8.7–616.6 μm). A little less than half of the particles is in the small size class (48.3%). Note that, assuming spherical particles, this means that the total volume in the small particle class is about 2.4×10^{-6} of the total volume of all expelled particles.

Sedimentation of fluid particles

A very basic description of sedimentation of fluid particles can be given by considering only gravitational and frictional forces

$$\begin{cases} m\ddot{x}(t) = -b\dot{x}(t) \\ m\ddot{y}(t) = -b\dot{y}(t) - mg \end{cases} \quad \begin{cases} x(0) = 0, \dot{x}(0) = a \\ y(0) = h, \dot{y}(0) = 0 \end{cases} \tag{5}$$

where x and y are horizontal and vertical distances, m is the mass of the fluid particle, g is the gravitational constant and b is a frictional coefficient. Initial height above the floor is h (m) and particles are expelled with initial horizontal velocity a (m/s). For spherical particles

$$m = \frac{4}{3}\pi r^3 \rho(\mathrm{kg}), \quad b = 6\pi\eta r\left(\mathrm{kg\ s^{-1}}\right) \tag{6}$$

where $\eta = 1.82\times10^{-5}$ ($\mathrm{kg\ m^{-1}\ s^{-1}}$) and $g = 9.81$ ($\mathrm{m\ s^{-2}}$). Eq. (5) can be solved to yield

$$x(t) = \frac{am}{b}\left(1-e^{-\frac{b}{m}t}\right); \quad y(t) = h - \frac{mg}{b}t + \frac{m^2 g}{b^2}\left(1-e^{-\frac{b}{m}t}\right) \tag{7}$$

so that the time a particle is suspended can be estimated (Fig. 2a). For a given initial velocity the horizontal distance travelled appears to only depend on particle diameter in a fairly narrow range, from 40 μm to 1 mm (Fig. 2b).

A sedimenting particle is assumed to be expelled in a random direction within a cone shaped region (Tang et al., 2009) of solid angle α steradians (1 steradian corresponds to an apex angle of $\approx 65.5°$ in a cross-section of the cone). The surface area of the base of the cone (as a spherical cap) is

$$S_c = \alpha d^2 \tag{8}$$

when d is the horizontal distance travelled by the particle. See Fig. 3. The volume of the cone is approximately

$$V_c = \frac{\pi d^3}{3}\left(1-\frac{\alpha}{2\pi}\right) + \frac{\alpha^2 d^3}{4\pi}\left(1-\frac{\alpha}{6\pi}\right) \tag{9}$$

(Nicas and Sun, 2006; Atkinson and Wein, 2008).

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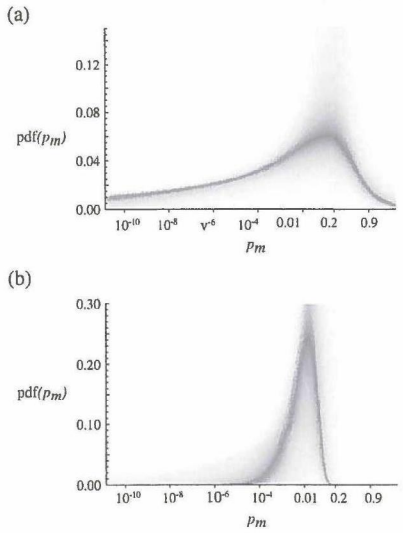

Fig. 7. Distribution of single virus unit infectivity for wild type influenza A virus, via aerosol inoculation and via intranasal droplet inoculation. Density chart determined from (posterior) predictive distribution of the infectivity parameters.

Inhalation of aerosol

If a person resides in a room with little ventilation where another infected person produces virus suspended in aerosol, the probability of inhaling a suspended particle (e.g. a droplet nucleus) is

$$P_{\text{inhal}}(\tau, Q_r, V_0) = 1 - e^{-\frac{Q_r \tau}{V_0}} \tag{10}$$

assuming perfect mixing, where V_0 is the room volume (m^3), Q_r is the respiration rate ($m^3\ s^{-1}$) and τ is the residence time, i.e. the average time the particle remains in suspension (as in Fig. 2a). It will be assumed that the respiration rate is 50 l/min and the room volume is $3\times4\times4 = 48\ m^3$. When the receiving subject remains in the room for a defined period T, say 1 h, the probability of inhalation is determined by $\text{Min}(\tau, T)$ instead of τ.

Droplet inoculation

In the same situation as above: a closed room with a person coughing, and another person who may be close enough to be exposed, the probability of contact with sedimenting infectious droplets may be considered. Above (sedimentation of fluid particles) the volume of space was calculated where an expelled droplet may be found (Eq. (9), see Fig. 3).

Assuming that contact with such a droplet may occur in a rectangular volume where the receiving person can be (in a room of $4\times4\ m^2$ a volume of approximately $2\times16 = 32\ m^3$) the probability of contact is proportional to $V_c/32$. A small fraction of the exposed body surfaces is mucosa (Nicas and Sun (2006) assume $15\ cm^2 = 15\times10^{-4}\ m^2$) and the probability of a droplet hitting exposed mucosa is proportional to $15\times10^{-4}/S_c$. The probability of contact through a sedimenting infectious droplet then is

$$P_{\text{droplet}} = \frac{15\times10^{-4}}{32}\frac{V_c}{S_c} = Kd \tag{11}$$

with d again the horizontal distance travelled by the droplet, and

$$K = \frac{15\times10^{-4}}{16\times9.6}\left(\frac{\pi}{3}\left(1-\frac{\alpha}{2\pi}\right) + \frac{\alpha^2}{4\pi}\left(1-\frac{\alpha}{6\pi}\right)\right)\frac{1}{\alpha} \tag{12}$$

where the solid angle α describes the dispersion in direction of sedimenting droplets.

Simulation of exposure

The following scenario was assumed: an infectious person produces droplets containing virus by coughing, with size distribution as in Fig. 1. The median horizontal velocity was assumed to be 2 m/s, its maximum (95 percentile) 12.5 m/s, and a gamma distribution was used to simulate its variation (parameters $r = 0.65$, $\lambda = 5.48$). Based on a hierarchical model analysis of nasal excretion data (Baccam et al., 2006) the concentration of virus was assumed to be lognormal with geometric mean 10^8 and 95% range 10^5–10^{12} (m^{-3}). At the time of coughing another person enters the room and remains there for 1 h, while there is neither little ventilation nor strong air movements.

The probabilities of exposure and infection (and acute symptoms of respiratory illness) were estimated for a single infectious particle (either sedimenting or non-sedimenting), and for a coughing attack consisting of a Poisson distributed number of coughs (15 coughs average) and negative binomially distributed numbers of particles per cough, average 466 (Loudon and Roberts, 1967), and dispersion parameter $p = 10$ (Teunis et al., 2008b). The resulting distribution of numbers of particles is shown in Fig. 10a.

Virus inactivation due to aerosol formation and drying was not accounted for because it is likely that the periods required are longer than the 1 h scenario assumed here. A reduction in infectivity of less than 1 log unit has been reported after 6 h suspension in air room temperature (Harper, 1961), at high humidity survival may be lower (Hemmes et al., 1960).

Results

Dose response assessment

The dose response relations for infection, illness among infected, and illness are shown in Figs. 4–6. These graphs show 'best fit' dose response relations for all individual isolates, as well as the (posterior) density of the predicted probabilities (of infection, illness given infection, or illness unconditionally). The latter densities can be thought of as estimates of infection or illness risk, generalized from the complete set of included dose response relations. The outer margins correspond to a 99% predictive interval. See online supporting information for more explanation and additional results. Also shown are the observed fractions, as far as these can be calculated.

The dose response relation for infection is completely determined by the infectivity of a single infectious unit (p_m in the model described above). Its distribution can also be determined, as shown in Fig. 7, for aerosol and intranasal droplet inoculation.

Aerosol inoculation of influenza A virus (Fig. 4a) results in high infectivity, mainly because of the responses to low doses (Jao et al., 1965; Alford et al., 1966).

Aerosol inoculation is about 20 times as efficient as intranasal droplets in causing infection, but with greater variability (Fig. 7).

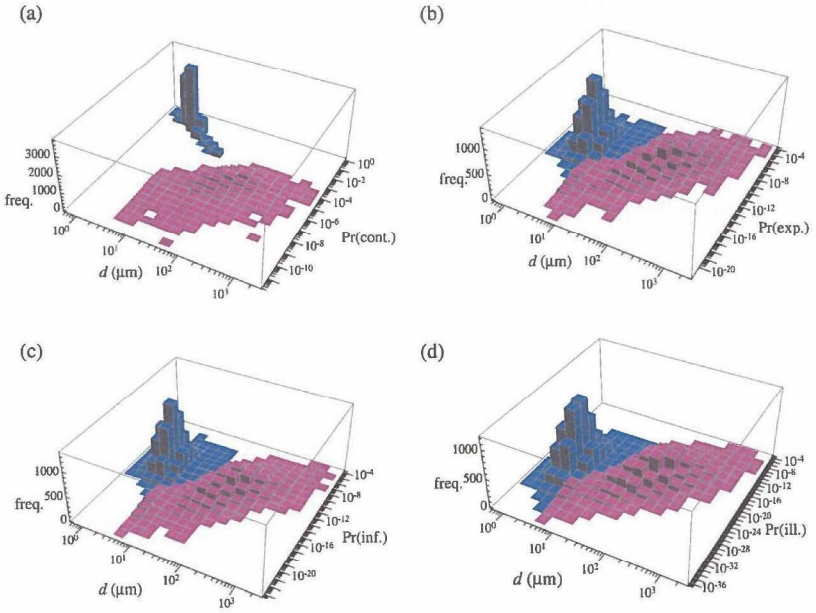

Fig. 8. Probabilities of contact with a fluid particle (a), exposure to infectious virus (b), infection (c), and symptoms of acute respiratory illness (d), as a function of the diameter of the expelled particle. Histograms for the two different transmission routes, aerosol inhalation and droplet inoculation, are shown in blue and red, respectively.

Simulated risk

Using the scenario outlined above a Monte Carlo simulation of the risks of exposure (i.e. inhalation or mucosal contact with at least one infectious virus particle) and infection can be simulated. The conditional dose response relations for acute illness among infected subjects may be used to also estimate illness risks.

The probability of contact with an expelled fluid particle as a function of its diameter is shown in Fig. 8a, for sedimenting and non-sedimenting particles. Also shown are the probabilities of exposure to virus, infection, and acute respiratory symptoms (Figs. 8b–d).

Fig. 9 shows risks associated with the presence of a single infectious particle, either non-sedimenting (aerosol) or sedimenting (droplet), with diameter drawn at random from the distribution defined by Loudon and Roberts (1967). The probability of exposure due to either transmission route is approximately equal, as is the infection risk. The probability of acute respiratory symptoms is higher with droplets, because the dose involved is likely to be higher. Note that the distribution of risk is highly skewed, with mean risks near the 95 percentile or even above that level.

The simulated risks associated with the production of a greater number of infectious particles is shown in Fig. 10, for the numbers of particles corresponding to a coughing attack.

Discussion

Previous studies on exposure issues in transmission of influenza have considered epidemic dynamics (Atkinson and Wein, 2008; Chen et al., 2009; Li et al., 2009) or not, dealing only with transmission mechanisms (Nicas and Sun, 2006; Nicas and Jones, 2009). All of these studies have ignored heterogeneity, both in virus infectivity (and pathogenicity) and in susceptibility of the human hosts. Use of a hierarchical framework has not only allowed us to use a two-parameter model that includes a (beta) distribution characterizing heterogeneity at the level of the single challenge study, but also to characterize the variation among studies, representing different virus isolates.

It should be noted that volunteers in human challenge studies usually are young adults in good general health, selected to not

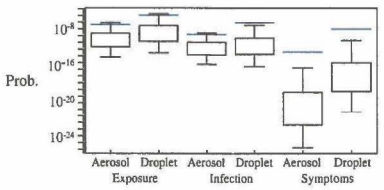

Fig. 9. Box plots of simulated risk of exposure to infectious virus, infection, and acute respiratory illness, when in the given scenario a single infectious particle is produced, either non-sedimenting (aerosol) or sedimenting (droplet). Boxes indicate quartiles, whiskers 95% ranges, and the horizontal lines indicate mean risks.

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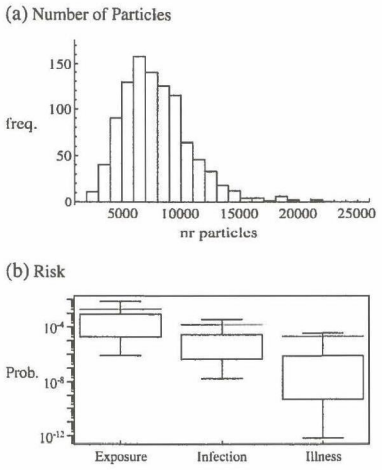

Fig. 10. Numbers of particles expelled in a coughing attack (a) and box plots of simulated risk of exposure to infectious virus, infection, and acute respiratory illness (b). Boxes indicate quartiles, whiskers 95% ranges, and the horizontal lines indicate mean risks.

develop severe illness. Although often the immune status of the volunteers is not known, especially in the older studies, the high observed infection and illness rates suggest low levels of immunity to infection or illness. In immune subjects the probability of illness (and possibly infection) is lower than in those with no immunity, given equal exposure. Therefore, when repeated exposure to similar virus strains is likely, the health risks may be lower than estimated here.

The dose response relation for illness among infected subjects implies that low dose exposure may lead to infection, due to the high infectivity of the virus, but of those infected only a small proportion may become ill. Exposure to high doses of virus results in most of the infected subjects also becoming ill. A shedding event releasing high numbers of viruses in the environment may therefore lead to clusters of cases that can be detected in disease surveillance. Where low numbers of viruses are present transmission may be mostly asymptomatic, and the odd person developing symptoms cannot easily be linked to other cases infected by the same source. When exposure to airborne virus is reduced, for instance by population-wide use of face masks, the relative decrease in numbers of illnesses is expected to be greater than the relative decrease in transmission, by numbers infected.

The quantitative characterization of influenza virus infectivity (and pathogenicity) provides a stronger basis for prospective studies of the effects of interventions, in particular those interventions that reduce exposure, for instance, the effect of face mask use on spread of pandemic influenza (Brienen et al., 2010).

In calculating the virus content of differently sized particles the virus concentration was assumed constant so that, given the virus concentration, the number of viruses in a particle of any size depends only on its volume. Sequestration of virus into fluid particles may however not be independent of particle size, and if this were the case the relative contributions of variously sized particles to exposure, infections and symptoms as shown in Fig. 7 may change.

It is worth noting here that virus in suspension may often be aggregated, causing the virus to be present in clumps of variable numbers of single viruses or virions, instead of a fully dispersed suspension of virions (Wei et al., 2007). If the inoculum should contain aggregates the effect on the dose response relation would be an increase in apparent heterogeneity (compared to a monodisperse suspension of the same virus): any suspended particle then may consist of 1 or more virions, each of variable infectivity (Teunis et al., 2008a).

In freshly shedded influenza virus most particles may be infectious: particle counts and $TCID_{50}$ do not differ greatly (Wei et al., 2007). Even the EID_{50}, the 50% infectious dose in chick embryo culture has been estimated to correspond to less than 10 particles, also supporting the assumption that $TCID_{50}$ and EID_{50} are approximately equal. However, when the virus has been exposed to environmental conditions the fraction infectious particles may decrease rapidly (Horsfall, 1954, 1955; Choppin and Tamm, 1960). Such loss of infectivity may not be important in the scenario considered here, but must be taken into account when considering exposure to virus in natural conditions.

The estimated probabilities of exposure and infection are within the same order of magnitude, indicating that one cannot readily discard either route as unimportant for transmission. The advantage of sedimenting droplets carrying a higher virus load is compensated by their smaller chance of contact combined with the lower infectivity of upper respiratory tract inoculation. Similarly, the more efficient inoculation of small aerosol particles is compensated by their smaller virus content. For example, outdoor aerosol transmission is not likely due to dilution and dispersion by ambient wind speeds and turbulence, whereas in closed environments, particularly with low ventilation, aerosol transmission is more likely.

Despite equal infection risks, the corresponding risks of acute respiratory illness are somewhat higher for droplets, due to the higher dose that is involved with larger particles.

Influenza virus may also be transmitted through hand contact with contaminated surfaces. Surface-to-hand-to-mucosa contacts were not considered in this study because the aim was to compare aerosol and droplet transmission in the absence of human behavioural factors, as these are poorly understood and the proximity of infectious and susceptible subjects cannot be easily quantified.

To improve the estimates of transmission of respiratory virus, further studies of exposure are needed, to determine how efficiently airborne virus may be transferred in the presence of ventilation, the relation between human contact behaviour and droplet infection, and most importantly, the role of contaminated surfaces in transmission of influenza.

Supplementary materials related to this article can be found online at doi:10.1016/j.epidem.2010.10.001.

Acknowledgments

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References

Alford, R.H., Kasel, J.A., Gerone, P.J., Knight, V., 1966. Human influenza resulting from aerosol inhalation. Proc. R. Soc. Exp. Biol. Med. 122 (3), 800–804.
Atkinson, M.P., Wein, L.M., 2008. Quantifying the routes of transmission for pandemic influenza. Bull. Math. Biol. 70 (3), 820–867.
Baccam, P., Beauchemin, C., Macken, C.A., Hayden, F.G., Perelson, A.S., 2006. Kinetics of influenza A virus infection in humans. J. Virol. 80 (15), 7590–7599.
Blachere, F.M., Lindsley, W.G., Pearce, T.A., Anderson, S.E., Fisher, M., Khakoo, R., Meade, B.J., Lander, O., Davis, S., Thewlis, R.E., Celik, I., Chen, B.T., Beezhold, D.H., 2009. Measurement of airborne influenza virus in a hospital emergency department. Clin. Infect. Dis. 48 (4), 438–440.
Brankston, G., Gitterman, L., Hirji, Z., Lemieux, C., Gardam, M., 2007. Transmission of influenza A in human beings. Lancet Infect. Dis. 7 (4), 257–265.
Brienen, N.C.J., [illegible], Wallinga, J., van Steenbergen, J.E., Teunis, P.F.M., 2010. The effect of mask use on the spread of influenza during a pandemic. Risk Anal. 30 (8), 1210–1218.

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Chen, S.C., Chio, C.P., Jou, L.J., Liao, C.M., 2009. Viral kinetics and exhaled droplet size affect indoor transmission dynamics of influenza infection. Indoor Air 19 (5), 401–413.

Choppin, P.W., Tamm, I., 1960. Studies of two kinds of virus particles which comprise influenza A2 virus strains: I. characterization of stable homogeneous substrains in reactions with specific antibody, mucoprotein inhibitors, and erythrocytes. J. Exp. Med. 112, 895–920.

Clements, M.L., O'Donnell, S., Levine, M.M., Chanock, R.M., Murphy, B.R., 1983. Dose response of A/Alaska/6/77 (H3N2) cold-adapted reassortant vaccine virus in adult volunteers: role of local antibody in resistance to infection with vaccine virus. Infect. Immun. 40 (3), 1044–1051.

Clements, M.L., Betts, R.F., Maassab, H.F., Murphy, B.R., 1984a. Dose response of influenza A/Washington/897/80 (H3N2) cold-adapted reassortant virus in adult volunteers. J. Infect. Dis. 149 (5), 814–815.

Clements, M.L., Betts, R.F., Murphy, B.R., 1984b. Advantage of live attenuated cold-adapted influenza A virus over inactivated vaccine for A/Washington/80 (H3N2) wild-type virus infection. Lancet 1 (8379), 705–708.

Clements, M.L., Snyder, M.H., Buckler-White, A.J., Tierney, E.L., London, W.T., Murphy, B.R., 1986. Evaluation of avian–human reassortant influenza A/Washington/897/80×A/Pintail/119/79 virus in monkeys and adult volunteers. J. Clin. Microbiol. 24 (1), 47–51.

Donald, H.B., Isaacs, A., 1954. Counts of influenza virus particles. J. Gen. Microbiol. 10, 457–464.

Duguid, J.P., 1946. The size and the duration of air-carriage of respiratory droplets and droplet nuclei. J. Hyg. Camb. 44 (6), 471–479.

Fabian, P., Mcdevitt, J.J., Dehaan, W.H., Fung, R.O.P., Cowling, B.J., Hung Chan, K., Leung, G.M., Milton, D.K., 2008. Influenza virus in human exhaled breath: an observational study. PLoS ONE 3 (7), e2691.

Haas, C.N., 1983. Estimation of risk due to low doses of microorganisms: a comparison of alternative methodologies. Am. J. Epidemiol. 118 (4), 573–582.

Harper, G.J., 1961. Airborne micro-organisms: survival tests with four viruses. J. Hyg. 59, 479–486.

Hatch, T.F., 1961. Distribution and deposition of inhaled particles in respiratory tract. Bacteriol. Rev. 25, 237–240.

Hemmes, J.H., Winkler, K.C., Kool, S.M., 1960. Virus survival as a seasonal factor in influenza and polimyelitis. Nature 188, 430–431.

Henle, W., Henle, G., Stokes, J., Maris, E.P., 1946. Experimental exposure of human subjects to viruses of influenza. J. Immunol. 52, 145–165.

Hirst, G.K., 1942. In vivo titrations of influenza virus and of neutralizing antibodies in chick embryos. J. Immunol. 45, 285–292.

Horsfall, F.L., 1954. On the reproduction of influenza virus; quantitative studies with procedures which enumerate infective and hemagglutinating virus particles. J. Exp. Med. 100 (2), 135–161.

Horsfall, F.L., 1955. Reproduction of influenza viruses; quantitative investigations with particle enumeration procedures on the dynamics of influenza A and B virus reproduction. J. Exp. Med. 102 (4), 441–473.

Jao, R.L., Wheelock, E.F., Jackson, G.G., 1965. Interferon study in volunteers infected with Asian influenza. J. Clin. Investig. 44 (6), 1062 Abstract, 57th Annual Meeting of the American Society for Clinical Investigation, Atlantic City, N.J., May 3, 1965.

Li, S., Eisenberg, J.N.S., Spicknall, I.H., Koopman, J.S., 2009. Dynamics and control of infections transmitted from person to person through the environment. Am. J. Epidemiol. 170 (2), 257–265.

Loudon, R.G., Roberts, R.M., 1967. Droplet expulsion from the respiratory tract. Am. Rev. Respir. Dis. 95 (3), 435–442.

Murphy, B.R., Chalhub, E.G., Nusinoff, S.R., Kasel, J., Chanock, R.M., 1973. Temperature-sensitive mutants of influenza virus. III. Further characterization of the ts-1[E] influenza A recombinant (H3N2) virus in man. J. Infect. Dis. 128 (4), 479–487.

Murphy, B.R., Sly, D.L., Hosier, N.T., London, W.T., Chanock, R.M., 1980. Evaluation of three strains of influenza A virus in humans and in owl, cebus, and squirrel monkeys. Infect. Immun. 28 (3), 688–691.

Murphy, B.R., Clements, M.L., Madore, H.P., Steinberg, J., O'Donnell, S., Betts, R., Demico, D., Reichman, R.C., Dolin, R., Maassab, H.F., 1984. Dose response of cold-adapted, reassortan influenza A/California/10/78 virus (H1N1) in adult volunteers. J. Infect. Dis. 149 (5), 816.

Murphy, B.R., Clements, M.L., Tierney, E.L., Black, R.E., Steinberg, J., Chanock, R.M., 1985. Dose response of influenza A/Washington/897/80 (H3N2) avian–human reassortant virus in adult volunteers. J. Infect. Dis. 152 (1), 225–229.

Nicas, M., Jones, R.M., 2009. Relative contributions of four exposure pathways to influenza infection risk. Risk Anal. 29 (9), 1292–2303.

Nicas, M., Sun, G., 2006. An integrated model of infection risk in a health-care environment. Risk Anal. 26 (4), 1085–1096.

Nicas, M., Nazaroff, W.W., Hubbard, A., 2005. Toward understanding the risk of secondary airborne infection: emission of respirable pathogens. J. Occup. Environ. Hyg. 2, 143–154.

Riley, R.L., 1974. Airborne infection. Am. J. Med. 57 (3), 466–475.

Riley, R.L., O'Grady, F., 1961. Airborne Infection: Transmission and Control. The Macmillan Company. New York.

Ryan, M.A., Christian, R.S., Wohlrabe, J., 2001. Handwashing and respiratory illness among young adults in military training. Am. J. Prev. Med. 21 (2), 79–83.

Sears, S.D., Clements, M.L., Betts, R.F., Maassab, H.F., Murphy, B.R., Snyder, M.H., 1988. Comparison of live, attenuated H1N1 and H3N2 cold-adapted and avian–human influenza A reassortant viruses and inactivated virus vaccine in adults. J. Infect. Dis. 158 (10), [redacted].

Snyder, M.H., Clements, M.L., Betts, R.F., Dolin, R., Buckler-White, A.J., Tierney, E.L., Murphy, B.R., 1986. Evaluation of live avian–human reassortant influenza A H3N2 and H1N1 virus vaccines in seronegative adult volunteers. J. Clin. Microbiol. 23 (5), 852–857.

Tang, J.W., Liebner, T.J., Craven, B.A., Settles, G.S., 2009. A schlieren optical study of the human cough with and without wearing masks for aerosol infection control. J. R. Soc. Interface 6 (Supplement 6), S727–S736.

Tellier, R., 2006. Review of aerosol transmission of influenza A virus. Emerg. Infect. Dis. 12 (11), 1657–1662.

Teunis, P.F.M., Havelaar, A.H., 2000. The beta Poisson model is not a single hit model. Risk Anal. 20 (4), 511–518.

Teunis, P.F.M., Nagelkerke, N.J.D., Haas, C.N., 1999. Dose response models for infectious gastroenteritis. Risk Anal. 19 (10), [redacted].

Teunis, P.F.M., Chappell, C.L., Okhuysen, P.C., 2002. *Cryptosporidium* dose response studies: variation between isolates. Risk Anal. 22 (1), 175–183.

Teunis, P.F., Moe, C.L., Liu, P., Miller, S.E., Lindesmith, L., Baric, R.S., Le Pendu, J., Calderon, R.L., 2008a. Norwalk virus: how infectious is it? J. Med. Virol. 80 (8), 1468–1476.

Teunis, P.F.M., Ogden, I.D., Strachan, N.J.C., 2008b. Hierarchical dose response of *E. coli* O157:H7 from human outbreaks incorporating heterogeneity in exposure. Epidemiol. Infect. 136 (6), 761–770.

Weber, T.P., Stilianakis, N.I., 2008. Inactivation of influenza A viruses in the environment and modes of transmission: a critical review. J. Infect. 57 (5), 361–373.

Wei, Z., McEvoy, M., Razinkov, V., Polozova, A., Li, E., Casas-Finet, J., Tous, G.I., Balu, P., Pan, A.A., Mehta, H., Schenerman, M.A., 2007. Biophysical characterization of influenza virus subpopulations using field flow fractionation and multiangle light scattering: correlation of particle counts, size distribution and infectivity. J. Virol. Meth. 144 (1–2), 122–132.

Xie, X., Li, Y., Chwang, A.T.Y., Ho, P.L., Seto, W.H., 2007. How far droplets can move in indoor environments—revisiting the Wells evaporation-falling curve. Indoor Air 17, 211–225.

Xie, X., Li, Y., Sun, H., Liu, L., 2009. Exhaled droplets due to talking and coughing. J. R. Soc. Interface 6 (Supplement 6), S703–S714.

Youngner, J.S., Treanor, J.J., Betts, R.F., Whitaker-Dowling, P., 1994. Effect of simultaneous administration of cold-adapted and wild-type influenza A viruses on experimental wild-type influenza infection in humans. J. Clin. Microbiol. 32 (3), 750–754.

ANNEX D

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The Effect of Mask Use on the Spread of Influenza During a Pandemic

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Face masks have traditionally been used in general infection control, but their efficacy at the population level in preventing transmission of influenza viruses has not been studied in detail. Data from published clinical studies indicate that the infectivity of influenza A virus is probably very high, so that transmission of infection may involve low doses of virus. At low doses, the relation between dose and the probability of infection is approximately linear, so that the reduction in infection risk is proportional to the reduction in exposure due to particle retention of the mask. A population transmission model was set up to explore the impact of population-wide mask use, allowing estimation of the effects of mask efficacy and coverage (fraction of the population wearing masks) on the basic reproduction number and the infection attack rate. We conclude that population-wide use of face masks could make an important contribution in delaying an influenza pandemic. Mask use also reduces the reproduction number, possibly even to levels sufficient for containing an influenza outbreak.

KEY WORDS: Influenza; mask use; pandemic; preparedness

1. INTRODUCTION

Pandemic preparedness involves implementation of both pharmaceutical (vaccination and antiviral drugs) and nonpharmaceutical countermeasures. As adequate pharmaceutical supplies will not be available immediately and may be insufficient for the total population, the WHO working group for public health interventions recommends nonpharmaceutical interventions as an important additional control measure.[1] Such measures fall into four groups, aiming to (1) limit international spread of the virus; (2) reduce spread within populations; (3) reduce the individual risk of infection (through personal protection and hygiene measures); and (4) raise public awareness of the risks.[2]

Masks have traditionally been used for centuries, for example, during the 17th-century plagues,[3] the 1918 influenza pandemic[4] and, more recently, the SARS epidemic in 2003. Retrospective case-control studies showed that mask use by the general public may have offered significant protection against SARS.[5,6] Nevertheless, no studies have assessed the efficacy of such mask use in preventing transmission of influenza viruses.[4]

This article addresses the following questions:

- What is the efficacy of mask use by healthy uninfected persons in protecting themselves against infection with influenza?

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- What might be the effect of population-wide mask use on the total impact of an influenza pandemic? Does it contain infection, delay spread, and/or reduce the total numbers of people infected?

Applying a mathematical model, we show that mask use at population level can play an important role in delaying and containing an influenza pandemic.

2. METHODS

2.1. Literature Search

A literature search using various search strategies was performed to answer the following questions:

- What are the characteristics of the main transmission routes of the influenza virus?
- What is the efficacy of mask use by a healthy person in preventing infection with influenza virus?

We applied two approaches to quantify infections, considering the risk of infection after exposure at the individual level and modeling the effect of population-wide mask use on transmission of infection (transmission modeling).

2.2. Virus Infectivity

For exploring the risk of individual infection after exposure, the single hit model of microbial infection[7] provides a general framework for studying the relation between exposure to a certain dose of virus and the probability of becoming infected (= $P_{inf.}$).

Experimental studies show that influenza A virus is more infectious in humans exposed by aerosol than in humans exposed by nasopharyngeal instillation of droplets.[2,8–10]

Aerosol inoculation of a few virus particles has been shown to potentially lead to infection while intranasal droplet inoculation requires several hundreds of viruses for infection. Nicas and Jones[11] infer that aerosol inoculation may be 3,200 times more efficient than intranasal inoculation, but because of the high uncertainty in their dose-response estimates they cannot exclude that these two inoculation routes are equally efficient.

If the virus is released in an entirely susceptible population (as during an influenza pandemic), the average number of secondary cases caused by any infectious subject during the complete infectious period (the basic reproduction number, R_0) is estimated to range from 1.5 to 3.0.[12–17]

2.3. Virus Transmission

To estimate the impact of face mask use by the public during an influenza pandemic, a deterministic SIR model was employed. Assuming pandemic spread of the virus, initial immunity was assumed to be absent.

The basic equation we used to predict the basic reproduction number R_0 of an influenza pandemic is:

$$R_0 = b \cdot \kappa \cdot D,$$

where b is the risk of transmission per contact, κ is the number of such contacts that an average person in the population would normally have per time unit (in the absence of any disease), and D is the duration of infectivity of an infected person, measured in the same time units as used for κ.[18]

Based on this equation, we estimated the effects of mask use (and the inherent reduction of $P_{inf.}$) on the R_0 of the pandemic.

The presumed effect of mask use was a decrease in the risk of acquiring infection during contact, depending on the filter efficiency (= M_{eff}) of the mask. In case of a low transferred dose it is likely that any decrease in exposure due to mask use causes an approximately proportional decrease in infection risk[19] and hence also in transmission of the virus. Given the high infectivity of the influenzavirus and its relatively low reproduction number, it seems likely that transmission may involve small doses of influenza virus.

Therefore, the probability of transmission per contact b will be reduced by this same fraction M_{eff} and thus R_0 will be reduced with this same fraction as well, on the condition that masks are properly used during all contacts. We will refer to this new R_0 that changes due to interventions as R_{int}.

Therefore,

$$R_{int} = (1 - M_{eff}) \cdot b \cdot \kappa \cdot D.$$

As masks will probably not be properly used during all contacts with the risk of transmission, we use the "mask coverage" within a population to indicate the proportion of mask use within this population. This mask coverage (= $M_{cov.}$) is defined as the proportion of contacts that are taking place with the proper use of a certain mask (compared to the total of all contacts within the population).

Only those who wear the mask properly are protected with its mask efficiency (M_{eff}). The remaining proportion ($1 - M_{cov}$) will not be protected by a mask. This changes the equation for the reproduction number to:

$$R_{int} = (1 - M_{eff} \cdot M_{cov}) \cdot R_0.$$

In estimating the possible effects of mask use on the infection attack rate we used the following equation:

$$a = 1 - e^{-a R_{int}}.$$

Here, the infection attack rate a is the proportion of the population that is infected after the first pandemic wave has passed through a completely susceptible population. During this first wave, the number of infectious contacts per infection is R_{int}, and the total number of infectious contacts during the wave per person is $a\,R_{int}$. Assuming random mixing, the probability that an individual is not contacted by any infectious person is $e^{-a R_{int}}$. Hence, the probability that an individual is contacted by at least one infectious person is $1 - e^{-a R_{int}}$. And because all individuals are susceptible at the start, this same term $1 - e^{-a R_{int}}$ also gives the probability that an individual is infected. This probability that an individual is infected is, by definition, equal to the infection attack rate a.

3. RESULTS

3.1. Transmission of Influenza

Influenza is spread mainly by direct or indirect contact transmission, droplet transmission, and aerosol transmission.

3.1.1. Contact Transmission

Contact transmission can occur as influenza viruses can survive on hard, nonporous surfaces (such as stainless steel and plastic) for 24–48 hours; on cloth, paper, and tissues for up to 8–12 hours; and (after transfer from these environmental surfaces) on hands for up to 5 minutes. However, the importance of contact transmission probably varies with the amount of virus present and the type of surface.[20]

The effect of mask use on contact transmission is unknown, but it seems reasonable that a face mask reduces contact transmission by preventing wearers from touching their mouths or noses with their hands or other objects potentially contaminated with virus. As face masks are not a standard intervention for the prevention of contact transmission, we focus in this study on the possible effect of mask use on the spread of influenza, transmitted by droplet or aerosol.

3.1.2. Droplet and Aerosol Transmission

Droplet and aerosol transmission occur when contagious droplets or aerosols are produced by an infected host during talking, coughing, or sneezing. Droplets are particles large enough to settle quickly, while aerosols are small enough to remain suspended in air for an indefinite period.[10] Fabian *et al.* showed that regular exhalation mainly results in aerosol production (>99% of exhaled particles <5 μm), with most people exhaling more than 500 particles per liter of air and influenza virus RNA being detected in the exhaled breath of 33% of influenza patients.[21]

Droplets smaller in diameter than a few micrometers are believed to evaporate to about half their initial size. These small liquid particles are usually referred to as "droplet nuclei."[22]

Many guidelines and review articles state that droplet transmission may be the main mode of influenza transmission. However, compelling scientific evidence supports the occurrence and significance of aerosol transmission[21,23] and suggests that it plays an important role in the spread of influenza[24] or may even be the dominant way of transmission.[25]

Certainly, the different features of droplets and aerosols may affect these types of transmission, thus influencing also the expected mask efficiency in either case. In Table I we summarize the main features for these two types of transmission.

Influenza virus administered via aerosol appears to be more infectious than via intranasal application of droplets, but this difference is difficult to quantify.[11]

In establishing the importance of droplet versus aerosol transmission for influenza, two more factors need to be considered. First, sedimenting droplets are bigger than nonsedimenting aerosols, thus containing more virus than an aerosol produced from the same virus suspension. For example, the volume of a particle with diameter 5 μm is 1,000 times smaller than the volume of a droplet of 50 μm, and thus likely contains a proportionally smaller number of virus particles. Second, virus in nonsedimenting aerosol resides in a closed (indoors) environment for hours while virus in sedimenting droplets remains suspended in air only for seconds after

Table I. Main Features of Aerosol Transmission Versus Droplet Transmission

Features	Aerosol Transmission	Droplet Transmission
Definition	Infection via inhalation of pathogen-carrying aerosol[22]	Infection via exposure to droplets sprayed by coughing or sneezing onto conjunctiva or mucous membranes[22]
Transmission vehicle	Aerosol	Droplet
Mean particle size (diameter) of transmission vehicle	$< 5\ \mu m$ in diameter[10,22] However, there is no consensus on the exact size criterion of an aerosol[22]	$> 10\ \mu m$[10,22] However, there is no consensus on the exact size criterion of a droplet[22]
Particle suspension time in the air	Sufficiently small to remain suspended in air for several minutes or more[10,22]	Do not stay suspended in the air but rapidly settle out[10,22]
Distance at which the virus can be spread	Can be disseminated by air currents throughout a room or facility[10]	Short distance[10]
Inoculation site	Lower respiratory tract is thought to be the main inoculation site[8–10]	Conjunctiva or mucous membranes[10,22]
Dose of virus required to induce infection	Low doses of virus may be sufficient[8]	Compared to aerosol inoculation, a higher dose of virus seems to be needed[8,9,11]
% of particles of this size emitted during exhalation	70% between 0.3 and $< 0.5\ \mu m$, 17% between 0.5 and $< 1\ \mu m$, and 13% between 1 μm and $< 5\ \mu m$[21]	$< 0.1\%$ of particles larger than $5\ \mu m$[21]
% of particles of this size emitted during cough or sneeze	Approximately equal numbers of particles in aerosol and droplet classes[22]	Most emitted pathogens are carried in droplets because of their greater volume[22]

expulsion. Aerosolized virus can be inhaled as long as a subject is in a room, whereas droplets have a much smaller time window during which they are accessible for deposition on mucosal surfaces. These three factors—higher infectivity of aerosolized virus, higher virus content of larger droplets, and longer residence times of smaller aerosols—tend to balance each other. Thus the dominance of droplet transmission versus aerosol transmission cannot be easily established.

3.2. Mask Efficiency in Virus Transmission

An overview of published studies on face mask protection against influenza viruses and or other respiratory viruses is shown in Table II.

Most of these studies focus on the efficiency of face masks in virus transmission when used during contact with patients, while only a few studies look into the possible reduction of infection risk when using a face mask in the general population.

For protection against nonbiological particles, standards specify the minimum requirements for different classes of masks.[35] Classifications depend mainly on the efficiency of the filter material and the maximum total inward leakage, that is, face-seal leakage, exhalation valve leakage, and filter penetration.[35] The testing procedures and criteria are standardized for a given laboratory setting and can differ from country to country. In order of increasing efficacy, these classes are the FFP1, FFP2, and FFP3 masks in Europe[35] and N95, N99, and N100 masks in the United States.[36]

Apart from these certified masks, there are many types of masks not certified as respiratory protective devices. Their exact protective effect against particles is unknown, as is their efficiency.

Van der Sande *et al.* showed that uncertified masks such as surgical masks and home-made masks can still give a considerable reduction in aerosol exposure.[37]

As Balazy *et al.* found that nonbiological particle simulants can be used to assess mask protection against biological particles of similar shape and size,[38] the minimum filtering efficiency of masks for nonbiological particles may be applied for virus-containing particles as well.

Mask efficiency for sedimenting droplets is likely to be better than for aerosol particles: proper mask use completely blocks droplet transmission to the mucous membranes of the upper respiratory tract, although it cannot prevent infection through the conjunctivae. We therefore presume mask protection factors for aerosols to represent a worst-case assumption for protection against droplets.

Table II. Overview of Published Studies on Face Mask Protection Against Influenza or Other Respiratory Viruses

Type of Study	Studied Viruses	Studied Population	Type of Mask Used	Results	Reference
Prospective case-control study	Influenza A and B	Hong Kong influenza patients and their household contacts	Surgical masks	• Influenza patients comply better with mask use than their contacts • Between 28 and 45% of influenza patients wearing mask "often or always" • 21% or less of contacts wearing mask "often or always"	26
Cluster randomized controlled trial	Influenza A and B	Hong Kong influenza patients and their household contacts	Surgical masks	• No significant difference was found between hand hygiene or hand hygiene plus face mask in household contacts of influenza patients • Hand hygiene and face masks can reduce influenza virus transmission if implemented early after symptom onset in an index patient • Only half of the influenza patients reported regular use of a surgical mask during follow-up; face mask adherence among household contacts was lower	27
Prospective case-control study	Influenza A, B, and other acute viral respiratory infections	Adult household contacts of a child with respiratory illness	Surgical masks, P2 masks	• Adherent mask use gives relative reduction of 60–80% in risk of acquiring a respiratory infection • < 50% of participants wearing the mask "most or all" of the time • No difference in adherence between P2 and surgical mask use	28
Case-control study	Influenza A, B, and RS-viruses	Dentists	Not specified	No marked reduction in infection	29
Observational study	Influenza and other acute viral respiratory infections	Lab respiratory specimens from Hong Kong population	***	• Possible association between population-based hygienic measures and reduced incidence • The relative contribution of each of these measures could not be estimated	30
Retrospective case-control study	SARS	Hong Kong citizens (probable SARS patients and matched controls)	Not specified	Using a mask frequently in public places was significant protective factor against SARS (OR = 0.27, $p < 0.001$ in multivariate analysis)	5

(*Continued*)

Table II. (*Continued*)

Type of Study	Studied Viruses	Studied Population	Type of Mask Used	Results	Reference
Retrospective case-control study	SARS	Beijing citizens (probable SARS patients and matched controls)	Not specified	• Wearing masks outside the home was significantly protective against SARS (OR = 0.3 for consistent mask use and OR = 0.4 for sometimes mask use, in multivariate analysis) • Many persons wearing masks in the community did not use N95 or similar highly efficient masks	6
Retrospective case-control study	SARS	Health care workers in 5 Hong Kong hospitals	Surgical masks, N95 masks, and paper masks	• The use of masks was significantly associated with noninfection (OR = 0.077, $p = 0.0001$) • Surgical and N95 masks were both effective, while paper masks did not significantly reduce the risk of infection	31
Retrospective cohort study	SARS	Nurses in 2 critical care units in Toronto	N95 masks and surgical masks	• Consistently wearing a mask while caring for a SARS patient was significantly protective against SARS (RR = 0.23, $p = 0.02$) • The data suggest that N95 masks offer better protection than surgical masks	32
Cohort study	RS-virus	New York hospital	Not specified	The use of masks does not seem warranted if other infection control procedures such as handwashing are used	33
Review	SARS	Health care workers	N95 masks and surgical masks	• In most studies, mask use was associated with a reduced risk of infection • It is still unclear whether N95 masks offered significantly better protection than surgical masks in all clinical situations	34

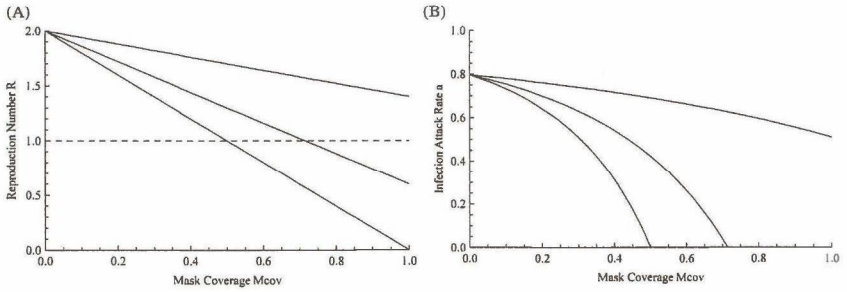

Fig. 1. (A) Effect of mask efficiency and mask coverage on the reproduction number R_{int}; upper line: $M_{eff} = 0.3$; middle line: $M_{eff} = 0.7$; lower line: $M_{eff} = 1.0$. (B) The effect of mask use on the infection attack rate; upper line: $M_{eff} = 0.3$; middle line: $M_{eff} = 0.7$; lower line: $M_{eff} = 1.0$.

3.3. Effect of Mask Use at Population Level

Assuming an R_0 of 2.0 during an influenza pandemic, we show in Fig. 1 the effect of mask coverage M_{cov} and mask efficiency M_{eff} on the value of the reproduction number R_{int} (Fig. 1A) and the infection attack rate (Fig. 1B).

A recent study shows that uncertified masks such as surgical masks and home-made masks used by untrained subjects may have a median protection factor of 2.4 to 6.5,[36] or a mask efficiency M_{eff} of 58–85%. In Fig. 1 we can see these masks can still give a considerable reduction of the reproduction number R_{int} and the infection attack rate.

Fig. 1A shows that, depending on mask efficiency and mask coverage, R_{int} might decrease below the threshold level of 1.0, effectively containing the pandemic.

These results are based on the reduction of aerosol exposure: the effect of mask use with droplet transmission is expected to be stronger.

4. DISCUSSION

This study attempts to predict the possible effects of population-wide mask use on the development of an influenza pandemic. Comparing aerosols (nonsedimenting particles) and droplets (sedimenting particles), we argue that in case of droplet transmission mask use may be at least as effective as for aerosol transmission.

Our results suggest that the use of face masks at the population level can delay an influenza pandemic, decrease the infection attack rate, and may reduce transmission sufficiently to contain the pandemic. The effect on final size of the epidemic depends on features of virus transmission, mask efficiency, and coverage of mask use in the population.

Our findings are based on data from published literature and mathematical models. As such models imply highly simplified situations in which only few variables can be studied, we focused on the effect of population-wide mask use in reducing the risk of infection in healthy individuals.

Additional effects, not included in the model, might render the effect of population-wide mask use even stronger than estimated in this study, as illustrated by the following three examples.

First, mask use not only protects healthy individuals but also reduces the infectiousness of symptomatic and asymptomatic carriers, thus reducing the number and effectiveness of transmission sources within the population. Since masks are not normally tested on their properties in preventing "outgoing infections," we did a separate study to estimate this secondary effect, and found considerably lower, but still measurable, retention factors,[37] indicating that masks worn by infectious subjects may increase the protective effect of population-wide use of face masks.

Second, mask use is expected to influence behavior. Wearing a mask can raise awareness of the infection risk and the importance of additional preventive behaviors such as more frequent hand-washing or avoiding physical contact and avoiding crowded public places. A face mask may also reduce contact

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transmission by preventing wearers from touching their mouths or noses with their hands or other objects potentially contaminated with virus.

However, on the other hand, face mask use might engender a false sense of security and lead to reduced use of other measures such as personal hygiene.

Finally, mask use is virtually the only way to prevent aerosol transmission, which may cause the most severe cases of influenza. Experimental aerosol inoculation displayed the spectrum of symptoms seen in natural infections, whereas experimental infection with intranasal drops produced milder disease, usually without involvement of the lower respiratory tract.[8–10,24] General sanitary interventions and social distancing can largely prevent transmission by contact and droplets, but is much less effective against transmission by aerosols.

The magnitude of such additional effects is unknown. More research on influenza transmission is needed to improve insight into the impact of mask use.

This study is based on the features (infectivity, route of transmission) most commonly expected in influenza. Changes in these features can change the effect of mask use within the population. If, for example, the pandemic virus spreads mainly by contact transmission, the preventive contribution of mask use might be small compared to routine hygienic measures.

We have not distinguished between different subpopulations (children vs. adults) or environments (open air vs. small rooms). If transmission depends more on some groups or environments than others, high mask coverage and mask efficiency within those groups or situations may have a disproportional effect on the course of the pandemic. The specification of such conditions depends on virus properties, such as transmission route and survival rate, and on host properties, such as risky behavior.

For example, we expect infectivity, mask efficiency, mask coverage, and virus transmission to be different for children than for adults. The impact of heterogeneity can only be estimated when more is known about the transmission features of the particular influenza virus and the specific risk groups for this virus. If small children (with a lower mask coverage and mask efficiency) play a more important role in transmission than adults, population-wide use of masks might be less effective than found in this study.

Mask efficiency might also be lower if the devices are used improperly or by people with aberrant face shapes or features such as facial hair. Respiratory protective devices are usually tested on healthy adult males who are clean-shaven. On the other hand, the mask efficiency indicated for a specific type of mask indicates the minimum needed for certification, and actual mask efficiency often exceeds the minimum.

Mask protection factors are characterized for nonbiological particles. Because even few pathogenic organisms passing through the filter may cause serious problems,[39] more information on infectivity and exposure is needed to refine our estimates of protection against respiratory infection.

Any outcome of a study like this mainly depends on the proportion of the population that is actually going to use a mask during an influenza pandemic. Past experience indicates considerable willingness to use face masks in case of such a threat. The proportion of people using masks in Hong Kong during the SARS epidemic ranged from 61.2%[40] to more than 90%.[5] Compliance with mask use in other times and other places to prevent other diseases is unknown but is expected to depend on the perceived threat of the pandemic.

In conclusion, the population-wide use of face masks can be a valuable strategy to delay or contain an influenza pandemic, or at least decrease the infection attack rate. We therefore strongly recommend including the use of face masks within pandemic control guidelines.

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REFERENCES

1. WHO consultation on priority public health interventions before and during an influenza pandemic. Geneva, Switzerland, 2004. Available at: http://www.who.int/csr/disease/avian_influenza/final.pdf, Accessed on May 2006.
2. World Health Organization writing group. Nonpharmaceutical interventions for pandemic influenza, international measures. Emerging Infectious Diseases, 2006; 12:81–87.
3. Zanderink R. Werken maskers nu wel of niet? Een speurtocht van enige eeuwen geleden tot heden? Nederlands Tijdschrift voor Anesthesiologie, 2003; 16:83–93.

4. World Health Organization writing group. Nonpharmaceutical interventions for pandemic influenza, national and community measures. Emerging Infectious Diseases, 2006; 12(1):88–94.
5. Lau JTF, Tsui H, Lau M, Yang X. SARS transmission, risk factors and prevention in Hong Kong. Emerging Infectious Diseases, 2004; 10:587–592.
6. Wu J, Xu F, Zhou W, Feikin DR, Lin CY, He X, Zhu Z, Liang W, Chin DP, Schuchat A. Risk factors for SARS among persons without known contact with SARS patients, Beijing, China. Emerging Infectious Diseases, 2004; 10:210–216.
7. Teunis P, Havelaar A. The beta poisson dose-response model is not a single-hit model. Risk Analysis, 2000; 20:513–520.
8. Alford RH, Kasel JA, Gerone PJ, Knight V. Human influenza resulting from aerosol inhalation. Proceedings of the Society for Experimental Biology and Medicine, 1966; 122:800–804.
9. Henle W, Henle G, Stokes J, Maris EP. Experimental exposure of human subjects to viruses of influenza. Journal of Immunology, 1945; 52:145–165.
10. Bridges C, Kuehnert M, Hall C. Transmission of influenza: Implications for control in health care settings. Clinical Infectious Diseases, 2003; 37:1094–1101.
11. Nicas M, Jones MJ. Relative contributions of four exposure pathways to influenza infection risk. Risk Analysis, 2009; 29:1292–1303.
12. Longini IM Jr, Halloran ME, Nizam A, Yang Y. Containing pandemic influenza with antiviral agents. American Journal of Epidemiology, 2004; 159:623–633.
13. Mills CE, Robins JM, Lipsitch M. Transmissibility of 1918 pandemic influenza. Nature, 2004; 432:904–906.
14. Ferguson NM, Cummings DA, Fraser C, Cajka JC, Cooley PC, Burke DS. Strategies for containing an emerging influenza pandemic in Southeast Asia. Nature, 2005; 437:209–214.
15. Ferguson NM, Cummings DA, Fraser C, Cajka JC, Cooley PC, Burke DS. Strategies for mitigating an influenza pandemic. Nature, 2006; 442:448–452.
16. Wallinga J, Lipsitch M. How generation intervals shape the relationship between growth rates and reproductive numbers. Proceedings. Biological Sciences/The Royal Society, 2006; 274:599–604.
17. Chowell G, [redacted], Bettencourt LM. Comparative estimation of the reproduction number for pandemic influenza from daily case notification data. Journal of the Royal Society, Interface/the Royal Society, 2007; 4:155–166.
18. Giesecke J. Mathematical models for epidemics. Pp. 119–132 in Giesecke J (ed). Modern Infectious Disease Epidemiology, 2nd ed. London: Arnold Publishers, 2002.
19. Teunis PFM, Nagelkerke NJD, Haas CN. Dose response models for infectious gastro-enteritis. Risk Analysis, 1999; 19:1251–1260.
20. Bean B, Moore BM, Sterner B, Peterson LR, Gerding DN, Balfour HH. Survival of influenza viruses on environmental surfaces. Journal of Infectious Diseases, 1982; 146:47–51.
21. Fabian P, McDevitt JJ, DeHaan WH, Fung RO, Cowling BJ, Chan KH, Leung GM, Milton DK. Influenza virus in human exhaled breath: An observational study. PloS One, 2008; 3:e2691.
22. Nicas M, Nazaroff W, Hubbard A. Toward understanding the risk of secondary airborne infection: Emission of respirable pathogens. Journal of Occupational and Environmental Hygiene, 2005; 2:143–154.
23. Morawska L. Droplet fate in indoor environments, or can we prevent the spread of infection? Indoor Air, 2006; 16:335–347.
24. Tellier R. Review of aerosol transmission of influenza A virus. Emerging Infectious Diseases, 2006; 12:1657–1662.
25. Weber T, Stilianakis NI. Inactivation of influenza A viruses in the environment and modes of transmission: A critical review. Journal of Infection, 2008;57:361–373.
26. Cowling BJ, Fung RO, Cheng CK, Fang VJ, Chan KH, Seto WH, Yung R, Chiu B, Lee P, Uyeki TM, Houck PM, Peiris JS, Leung GM. Preliminary findings of a randomized trial of non-pharmaceutical interventions to prevent influenza transmission in households. PloS One, 2008; 3:e2101.
27. Cowling BJ, Chan KH, Fang VJ, Cheng CK, Fung RO, Wai W, Sin J, Seto WH, Yung R, Chu DW, Chiu BC, Lee PW, Chiu MC, Lee HC, Uyeki TM, Houck PM, Peiris JS, Leung GM. Facemasks and hand hygiene to prevent influenza transmission in households. Annals of Internal Medicine, 2009; 151:437–446.
28. MacIntyre CR, Cauchemez S, Dwyer DE, Seale H, Cheung P, Browne G, Fasher M, Wood J, Gao Z, Booy R, Ferguson N. Face mask use and control of respiratory virus transmission in households. Emerging Infectious Diseases, 2009; 15:233–241.
29. Davies KJ, Herbert A-M, Westmoreland D. Seroepidemiological study of respiratory virus infections among dental surgeons. British Dental Journal, 1994; 176:262–265.
30. Lo JY, Tsang TH, Leung YH, Yeung EY, Wu T, Lim WW. Respiratory infections during SARS outbreak, Hong Kong, 2003. Emerging Infectious Diseases, 2005; 15:1738–1741.
31. Seto WH, Tsang D, Yung RW, Ching TY, Ng TK, Ho M, Ho LM, Peiris JS; Advisors of Expert SARS group of Hospital Authority. Effectiveness of precautions against droplets and contact in prevention of nosocomial transmission of severe acute respiratory syndrome (SARS). Lancet, 2003; 362:1519–1520.
32. Loeb M, McGeer A, Henry B, Ofner M, Rose D, Hlywka T, Levie J, McQueen J, Smith S, Moss L, Smith A, Green K, Walter SD. SARS among critical care nurses, Toronto. Emerging Infectious Diseases, 2004; 10:251–255.
33. Hall C, Douglas G. Nosocomial respiratory syncytial viral infections. Should gowns and masks be used? American Journal of Diseases of Children, 1981; 135:512–515.
34. Gamage B, Moore D, Copes R, Yassi A, Bryce E; BC Interdisciplinary Respiratory Protection Study Group. Protecting health care workers from SARS and other respiratory pathogens: A review of the infection control literature. American Journal of Infection Control, 2005; 33:114–121.
35. NEN: Nederlands Normalisatie-instituut. Nederlandse norm NEN-EN 149 (en): Ademhalingsbeschermingsmiddelen – Filtrerende halfmaskers ter bescherming tegen deeltjes – Eisen, beproeving, merken. 2001.
36. National Institute for Occupational Safety and Health. NIOSH-Approved Disposable Particulate Respirators (Filtering Facepieces). Available at: http://www.cdc.gov/niosh/npptl/topics/respirators/disp_part/, Accessed on May 2006.
37. Van Der Sande M, Teunis P, Sabel R. Professional and homemade face masks reduce exposure to respiratory infections among the general population. PloS One, 2008; 3:e2618.
38. Balazy A, Toivola M, Adhikari A, Sivasubramani SK, Reponen T, Grinshpun SA. Do N95 respirators provide 95% protection level against airborne viruses, and how adequate are surgical masks? American Journal of Infection Control, 2006; 34:51–57.
39. Rengasamy A, Zhuang Z, Berry Ann R. Respiratory protection against bioaerosols: Literature review and research needs. American Journal of Infection Control, 2004; 32:345–354.
40. Tang CS, Wong CY. Factors influencing the wearing of facemasks to prevent the severe acute respiratory syndrome among adult Chinese in Hong Kong. Preventive Medicine, 2004; 39:1187–1193.

ANNEX E

(10)(2e) <(10)(2e)@bijdegelijk.com>

RE: Toegang houden tot dagelijkse COVID-19 Data

1 message

covid-19 surveillance <(10)(2e)@rivm.nl> Tue, Aug 11, 2020 at 5:07 PM
To: "(10)(2e)@bijdegelijk.com" <(10)(2e)@bijdegelijk.com>
Cc: EPI-datamanagement <(10)(2e)@rivm.nl>

Beste (10)(2e),

Bij deze antwoorden op uw vragen. In de open data op https://data.rivm.nl/geonetwork/srv/dut/catalog.search#/metadata/2c4357c8-76e4-4662-9574-1deb8a73f724?tab=relations en in het wekelijkse pdf rapport https://www.rivm.nl/documenten/wekelijkse-update-epidemiologische-situatie-covid-19-in-nederland is overigens veel van de onderstaande gevraagde data terug te vinden.

1. Het is mij niet geheel duidelijk over welke data/aantallen het hier gaat, maar ik ga ervan uit dat dit de bovengenoemde open data betreft. Hierin wordt de datum als date_statistics vermeld. Dit houdt in dat het de datum van de eerste ziektedag kan zijn. Als die datum ontbreekt, is het de datum van de labuitslag. Wanneer ook die ontbreekt, is het de datum van melding aan de GGD.
2.
    1. De incubatietijd is inderdaad 5-6 dagen, zie https://www.rivm.nl/coronavirus-covid-19/ziekte
    2. Wij hebben hier zelf geen data van, dus u kunt hiervoor het beste de literatuur raadplegen.
    3. Vanaf 27 februari zijn er 11.994 opnames gemeld van de in totaal 59.973 aan de GGD'en gemelde COVID-19 patiënten. Dit is 20% (figuur 12.2.1 weekrapport) en https://data.rivm.nl/geonetwork/srv/dut/catalog.search#/metadata/2c4357c8-76e4-4662-9574-1deb8a73f724?tab=relations
    4. Data over COVID-19 patiënten die op de IC worden opgenomen is te vinden op https://www.stichting-nice.nl/ Vandaag is het cumulatieve aantal COVID-19 patiënten op de IC 2.946. Van een totaal van 59.973 patiënten is dat dus 5%.
    5. Vanaf 27 februari zijn er 6.159 COVID-19 patiënten overleden de in totaal 59.973 aan de GGD'en gemelde COVID-19 patiënten. Dit is 10% (figuur 12.2.1 weekrapport) en https://data.rivm.nl/geonetwork/srv/dut/catalog.search#/metadata/2c4357c8-76e4-4662-9574-1deb8a73f724?tab=relations
    6. Wij berekenen dit op basis van de meldingsdata van de GGD'en en stichting NICE data (ICs). Dit zijn gegevens die dagelijks worden bijgewerkt, daardoor veranderen deze waarden en is er geen vaste waarde voor.
    7. Zie hier meer informatie over viral load https://www.ecdc.europa.eu/en/covid-19/latest-evidence/transmission https://www.thelancet.com/action/showPdf?pii=S2213-2600%2820%2930354-4 https://lci.rivm.nl/covid-19-testbeleid%20personen%20zonder%20klachten
    8. Het hele testsysteem is (tot nu toe) gericht op het testen van symptomatische patiënten. Om deze reden hebben wij geen systematisch inzicht in geïnfecteerde mensen die asymptomatisch of presymptomatisch zijn. Hiervoor kunt u dus het beste de literatuur raadplegen.

Ik ga ervan uit uw vragen zo voldoende beantwoord te hebben.

Vriendelijke groeten,

(10)(2e)

Namens COVID-19 surveillance team

ANNEX F

De volgende partijen hebben desbetreffende correspondentie ontvangen.

voor Z.M. Koning Willem-Alexander Paleis Noordeinde Postbus 30412 2500 GK Den Haag	De Minister-president Minister Mark Rutte Ministerie van Algemene Zaken Postbus 20001 2500 EA Den Haag
RIVM (10)(2e) (10)(2e) (10)(2e) (10)(2e) (10)(2e) Postbus 1 3720 BA Bilthoven	Ministerie van Volhsgezondheid, Welzijn en Sport Minister Huge de Jonge Postbus 20350 2500 EJ Den Haag
Veiligheidsberaad Hubert Bruls Postbus 7010 6801 HA Arnhem	Veiligheidsregio Amsterdam-Amstelland F. Halsema Postbus 92171 1090 AD Amsterdam
Veiligheidsregio Rotterdam-Rijnmond A. Aboutaleb Postbus 9154 3007 AD Rotterdam	Veiligheidsregio Gooi en Vechtstreek P.I. Broertjes Kamerlingh Onnesweg 148 1223 JN Hilversum
Veiligheidsregio Noord-Holland Noord P.M. Bruinooge Postbus 416 1800 AK Alkmaar	Veiligheidsregio Gelderland-Zuid H.M.F. Bruls Postbus 1120 6501 BC Nijmegen
Veiligheidsregio Fryslân S. Buma Postbus 612 8901 BK Leeuwarden	Veiligheidsregio Zaanstreek-Waterland J. Hamming Postbus 150 1500 ED Zaandam
Veiligheidsregio Kennemerland M. Schuurmans Postbus 5514 2000 GM Haarlem	Veiligheidsregio Brabant-Zuidoost (VRBZO) J. Jorritsma Postbus 242 5600 AE Eindhoven
Veiligheidsregio Zuid-Holland Zuid A.W. Kolff Postbus 350 3300 AJ Dordrecht	Veiligheidsregio Haaglanden J.H.C. van Zanen Dedemsvaartweg 1 2545 AP Den Haag

Veiligheidsregio Hollands Midden H.J.J. Lenferink Postbus 1123 2302 BC Leiden	Veiligheidsregio Zeeland J.A.H. Lonink Postbus 8016 4330 EA Middelburg
Veiligheids- en Gezondheidsregio Gelderland-Midden A. Marcouch Postbus 5364 6802 EJ Arnhem	Veiligheidsregio IJsselland P.H. Snijders Postbus 1453 8001 BL
Veiligheidsregio Brabant-Noord J. Mikkers Postbus 218, 5201 AE 's-Hertogenbosch	Veiligheidsregio Groningen K.F. Schuiling Postbus 66, 9700 AB Groningen
Veiligheidsregio Drenthe M.L.J. Out Postbus 402 9400 AK Assen	Veiligheidsregio Limburg-Noord A.S. Scholten Postbus 11 5900 AA Venlo
Veiligheidsregio Zuid-Limburg J.M. Penn-te Strake Postbus 35 6269 ZG Margraten	Veiligheidsregio Twente G.O. van Veldhuizen Postbus 383 7500 AJ Enschede
Veiligheidsregio Flevoland F.M. Weerwind Postbus 501 8200 AM Lelystad	Veiligheidsregio Midden- en West-Brabant Th. Weterings Postbus 3208 5003 DE Tilburg
Veiligheidsregio Utrecht P.E.J. den Oudsten Postbus 3154 3502 GD Utrecht	GGD GHOR Nederland (10)(2e) Zwarte Woud 2 3524 SJ Utrecht