Best Evidence Topic Report 23

Titel:

Welke isolatiemaatregelen zijn nodig bij patiënten met een vermoeden van COVID-19 in de praktijk?

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Antwoord op klinische vraag:

Op basis van deze studies (voornamelijk over influenza) moet sociale distancing zo snel mogelijk na de aankondiging van het eerste geval in een land worden geïmplementeerd. Het succes van deze interventie neemt af als deze niet onmiddellijk wordt uitgevoerd (voor een R0 = 2,5; vertragingen van 2, 3 en 4 weken resulteerden in definitieve aanvalspercentages van respectievelijk 7%, 21% en 45%) en, volgens een ander onderzoek, zou na 3 weken nauwelijks effect hebben. Het effect van social distancing hangt ook af van de epidemiologische aard van het virus; aangezien de R0 van COVID-19 hoger is dan die van influenza, zal social distancing een kleiner effect hebben. Social distancing moet worden gecombineerd met andere preventieve maatregelen zoals handhygiëne en moet gedurende een voldoende lange periode worden gehandhaafd; één studie suggereerde zelfs een nadelig effect op de virale verspreiding als de social distancing te vroeg werd gestopt.

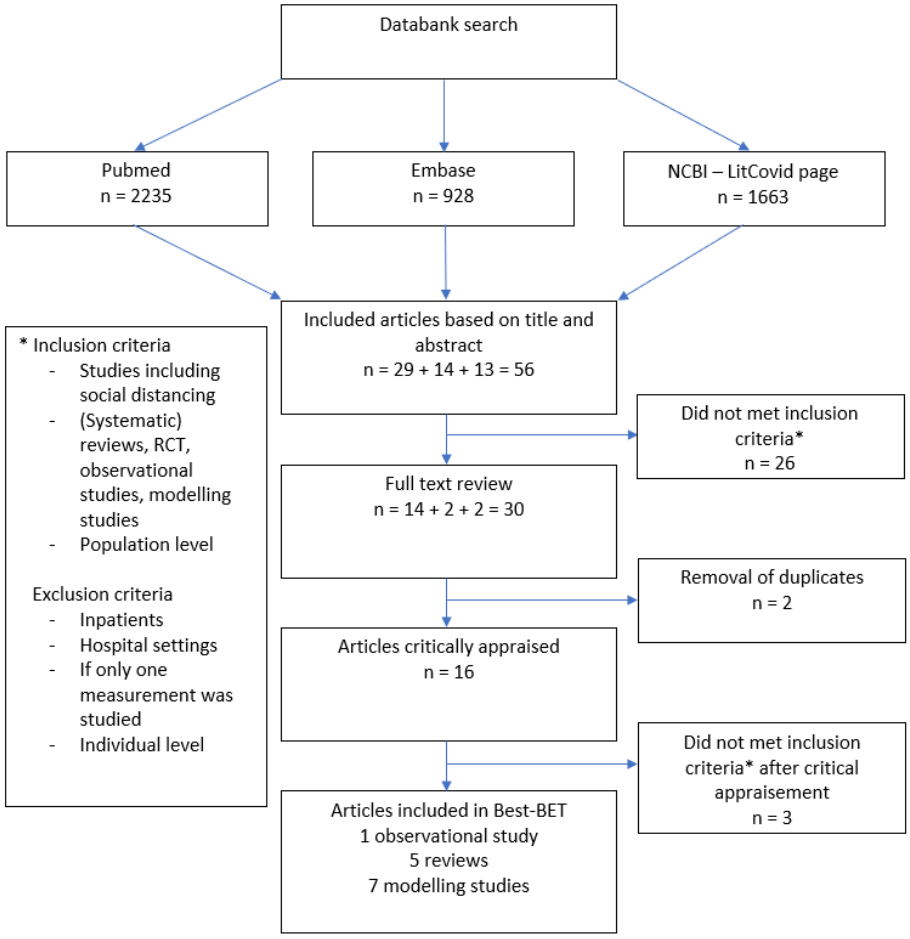
Disclaimer:

Deze rapporten zijn ontwikkeld volgens de methode van de Best Evidence Topics, kortweg bestBETs. Een bestBET beoogt een antwoord te geven op een specifieke klinische vraag, geformuleerd op basis van het op dit ogenblik best beschikbare bewijs. Omwille van de beperkte beschikbaarheid van wetenschappelijk bewijs voor COVID-19 topics, worden ook studies van lagere kwaliteit gebruikt. BestBETs bevatten geen aanbevelingen. Studenten 3e Master geneeskunde van de KU Leuven werkten deze topics uit onder begeleiding van twee docenten, waarna ze volgens een vast stramien een eindrapport opstellen. Voor de validatie van deze rapporten, konden we beroep doen op de expertise van CEBAM, die de rapporten rigoreus toetste aan vooropgestelde kwaliteitscriteria.

Best evidence topic

Title	**Isolation measures of suspected COVID-19 patients in practice**
Report by	Marie-Laure Bonte & Louis Bourgeois
Search checked by	Prof. Dr. Cathy Matheï
Clinical scenario	Due to the recent complications concerning the covid-19 pandemic, there is an urgent need for guidelines to contain the spread of the virus. Social distancing is the reduction of social activities (including school and workplace closure, travel restrictions and restrictions of mass gatherings) and avoiding physical contact with others or maintaining a physical distance during necessary contacts. Can social distancing help to contain the virus and prevent further spread?
Answerable question (PICO/PIRT/PEO/…)	P: Suspected COVID-19 patients in practice I: Social distancing (reducing social activities and amount of physical contact) C: No social distancing O: Preventing further spread of COVID-19
Search terms	1. Pubmed: (((((((((coronavirus, sars[MeSH Terms]) OR ards, human[MeSH Terms]) OR human influenza[MeSH Terms]) OR acute respiratory distress syndrome[MeSH Terms]) OR infections, upper respiratory[MeSH Terms]) OR infections, lower respiratory[MeSH Terms]) OR atypical pneumonia, primary[MeSH Terms]) AND quarantine[MeSH Terms]) AND epidemic[MeSH Terms]) OR pandemic[MeSH Terms] 2. Embase: (COVID-19 OR Coronavirus OR severe acute respiratory syndrome OR SARS OR MERS OR influenza OR viral respiratory infection OR ARDS OR epidemic) AND human AND (quarantine OR social distancing OR isolation) 3. LitCovid databank
Search date	18/03/2020 - 27/03/2020
Search outcome (number of hits)	4826
Relevant papers (number of final inclusions)	5 reviews, 1 observational study, 7 modelling (simulation) studies

Flow chart


Databank search
Pubmed
n = 2235
Embase
n = 928
NCBI – LitCovid page
n = 1663
Included articles based on title and abstract
n = 29 + 14 + 13 = 56
Did not met inclusion criteria*
n = 26
Full text review
n = 14 + 2 + 2 = 30
Removal of duplicates
n = 2
Articles critically appraised
n = 16
Did not met inclusion criteria* after critical appraisement
n = 3
Articles included in Best-BET
1 observational study
5 reviews
7 modelling studies
* Inclusion criteria
- Studies including social distancing
- (Systematic) reviews, RCT, observational studies, modelling studies
- Population level
Exclusion criteria
- Inpatients
- Hospital settings
- If only one measurement was studied
- Individual level

Author, date, country	Patient group	Study type	Outcomes	Results	Study weaknesses
Lau et al. 2020, California USA (1)	Population in Wuhan, China.	Observational study	Correlation of domestic air traffic to the number of confirmed COVID-19 cases. Growth curves of COVID-19 cases within China before and after lockdown as well as after changes in COVID-19 diagnostic criteria.	Significant increase in doubling time from 2 days to 4 days after imposing lockdown. The correlation between domestic air traffic and COVID-19 spread became weaker following lockdown.	This data cannot differentiate which of the stringent measures were most successful, as our analyses only assessed the efficacy of the totality of these measures.
Jefferson et al. 2011, Italy (2)	People of all ages	Systematic review and meta-analysis	Numbers of cases of viral illness.	Global measures, such as screening at entry ports, led to a non-significant marginal delay in spread. There was limited evidence that social distancing was effective, especially if related to the risk of exposure.	Heterogenous set of observations/patient groups. Hard to make a general conclusion for this population. Lack of description of randomisation sequence, concealment or allocation within included studies. Reporting bias: selective reporting within included studies. Attrition bias: incomplete outcome of data within included studies.

Ahmed et al. 2018 Atlanta, GA, USA (3)	Randomized controlled trials, epidemiological studies, and modelling studies reporting results of social distancing interventions in non-healthcare workplaces.	Systematic review	Cumulative influenza attack rate. Peak influenza rate. Time to peak. Lost workdays. Any harms.	Modelling studies support social distancing in non-healthcare workplaces, but there is a paucity of well-designed epidemiological studies. Social distancing measure alone produced a median reduction of 23% in the cumulative influenza attack rate in the general population. It also delayed and reduced the peak influenza attack rate. Effectiveness was reported to be greater when workplace social distancing was combined with other nonpharmaceutical or pharmaceutical interventions.	High risk of bias in all 3 included epidemiological studies. The quality of all 12 modelling studies was not assessed.
Rashid et al. 2015, Australia (4)	80 studies, not further specified.	Systematised review	The role of social distancing measures (school closure, workplace closure or home working, restriction of mass gathering) against an influenza pandemic.	School closure was considered to be moderately effective but with high variance between studies. The effectiveness of workplace closure or home working strategies were modest effective and highly acceptable. However, high levels of workplace closure (at least 33%) combined with 100% school closure was required in a modelling study to mitigate a pandemic. Some evidence suggests that mass gatherings can amplify influenza transmission, especially if the event takes place shortly before the epidemic peak but available data provide little support for reduced transmission from cancelling mass gatherings.	This review is rather a narrative review, the inclusion criteria for the studies are not mentioned. Overall, the quality of the evidence was quite weak, drawing primarily on observational or simulated data.

				Overall, social distancing measures appear modestly effective and many are likely to be acceptable in the short term, but there is a lack of strong evidence.	
Lee et al. 2009 Singapore (5)	19 modelling studies.	Systematic review	Cumulative influenza attack rate (overall and peak attack rate)	Social distancing measures (including school closure, workplace and community social distancing, travel cancelling) alone reduces the overall attack rate significantly. But the combination with other prevention measures (such as antiviral prophylaxis, case isolation and contact tracing) reduces the overall attack rate and the peak attack rate even more.	The restriction of the searches to the PubMed database only Other intrinsic limitations of modelling studies exist, and include the fact that they are based on theoretical epidemiology and not fully based on clinical or epidemiological evidence.
Aledort et al. 2007, California USA (6)	168 articles: 9 systematic reviews, 49 narrative reviews, 3 RCTs, 29 observational studies, 12 mathematical models, 30 case reports, 9 evidence based guidelines, 27 expert opinions.	Literature review	The role of non-pharmaceutical interventions (mandatory social distancing measures) for an influenza pandemic.	Modelling studies generally support school closure and confinement in the home as an effective means of reducing overall attack rates within communities when coupled with antiviral prophylaxis, but predicting the effect of closing schools and workplaces is difficult, since infectious individuals may be displaced into other settings. Models suggest that cancellation of non-essential public gatherings and restrictions on long-distance travel might help to decrease rates of transmission and overall morbidity, but the effectiveness of these interventions has not been quantified.	Not a systematic review. Very little of the literature is on point, and the experts disagreed 60 percent of the time.

Modelling studies

Author, date, country	Patient group	Study type	Outcomes	Results	Study weaknesses
Fang et al., Feb 2020, China (7)	Data obtained from National Health Commission of the People's Republic of China, Chinese Center for Disease Control and Prevention, WHO, and various websites of Chinese government agencies, official media and previous studies.	Data-analysis Using the SEIR: an epidemic model that can reflect the flows of peoples between four states: susceptible, exposed, infectious and recovered.	Simulation of the spread dynamics of the COVID-19 disease outbreak.	Rigorous government control policies were associated with a slower increase in the infected population, but the optimization of therapeutic strategy and the development of specific drugs would be of more importance than quarantine and protective procedures as more cases accrue.	This study was made in the stage of much uncertainty about COVID-19, so the accuracy and precision of this model might not be very good. There must be some unavoidable discrepancy between the confirmed patients and the actual numbers, which lead to an inevitable deviation in the estimations.
Lee et al. 2018, Seoul Republic of Korea (8)	Population of South Korea	Metapopulation model Simulation of spatial-temporal pattern of spread of the 2009 H1N1 influenza virus (no available vaccines or antiviral therapy)	Reduction rate of cumulative incidence of 2009 H1N1 influenza infections	Non-pharmaceutical interventions like isolation (can include the quarantine of contacts, closure of schools, cancellation of mass gatherings, and use of masks in public as well as the isolation of influenza patients) and commuting restrictions are an excellent strategy for incidence reduction, as the cumulative incidence reduced by 14–23% in all seven integrated regions, although 20% isolation and 20% commuting restrictions were only implemented over two weeks as the first case occurred at the source of the local outbreak. Early intervention at the source area of infection is more effective than interventions	Uses only demographic data of Republic of Korea to simulate 2009 H1N1 influenza outbreak

				at the commuting-hub areas if the cost is limited.	
Yang et al. 2011, Michigan USA (9)	The whole population of a small city in the Netherlands (Eemnes) consisting of 8382 people, 3.2% were 4 years old or younger, 3.5% were between 5 and 9, 6.4% were between 10 and 17, 71.3% were between 17 and 64, and 15.6% were 65 years or older.	Individual Space-Time Activity-based Model (ISTAM)	Simulate the effectiveness of non-pharmaceutical control measures for an influenza outbreak, including: (1) refraining from social activities, (2) school closure and (3) household quarantine.	From the ISTAM model, school closure resulted in about a 4.2% reduction in the total number of cases and a 28.9% reduction in the peak number of cases. With school closure, infection in schools was reduced to a very low level, but infection within other regions increased in absolute number. This research highlighted the importance of combining control measures. School closure alone was not particularly effective, but when combined with home quarantine, it reduced the total number of cases more than the sum of these two control measures alone. It should be noted that although the three control measures are applicable to different levels of aggregation (refraining from social activity is applicable to individuals, household quarantine is applicable to all members within households and school closure is applicable to all students), they are not independent of each other.	They did not include the possibility that disease agents may stay suspended in the air or survive on some surfaces such as door handles for an extended period of time. It was not possible to validate the model directly due to the lack of historical data on the impact of non-pharmaceutical control measures on disease outbreaks in Eemnes. No certainty if household quarantine was based on population level or case level.
Duerr et al. 2007, Stuttgart Germany (10)	Demographic and public health parameters which represent the situation in Germany in 2006.	Planning tool InfluSim, a deterministic compartment model based on a system of over thousand differential equations	Examine how social distancing measures determine the course of an influenza pandemic wave and its success.	The peak of the epidemic is protracted by about 1 day for every percent of contact reduction if this intervention starts immediately after the introduction of the infection. Thus, a peak shift is not only possible by early action, but also by the degree of contact reduction. If contact reduction is initiated later, the peak shift diminishes, but the proportionality remains.	In the preceding analyses it was assumed that parameter values are precisely known; in a real world scenario, however, uncertainty arises from biological variability, stochastic influences, heterogeneities, etc.

				Premature cessation of contact reduction measures restores the infection rates to the pre-intervention values which fuels the epidemic. It can lead to a delayed course and a higher total number of infections, involving a plateau or even a second peak of the epidemic.	
Lee et al. 2015, Republic of Korea (11)	Population of the Seoul Metropolitan Area (SMA) (2009)	Spatial–temporal influenza model	Analysing the spread patterns of 2009 influenza A/H1N1 in the SMA by the reproductive numbers and geographic information systems. Investigating the impact of non-pharmaceutical public health interventions, isolation (isolation of influenza patients, quarantine of contacts, closure of schools, cancellation of mass gatherings, and use of masks in public) and/or commuting restrictions, on the incidence reduction in various scenarios.	Isolation alone is an inefficient measure in all but 2 districts. In Gwacheon provides this intervention a strong impact on incidence reduction. Period and starting date of isolation have no effect on incidence reduction after approximately 3 weeks. Commuting restrictions in Gwacheon alone leads to an effective incidence reduction, which is observed in all districts except Gwacheon. Earlier intervention is the best strategy and the commuting restrictions will have no effect after 4 weeks. The combined implementation of isolation and commuting restrictions in Gwacheon was an excellent strategy for incidence reduction, as the incidence rates reduced by 14–26% in all 33 districts within the SMA, although 20% isolation and 20% commuting restrictions were only implemented in Gwacheon.	This model is based on specific demographic data of the SMA.
Kelso et al. 2009, Perth Australia (12)	A real community with a population of	Individual-based model	Four intervention methods for an influenza pandemic	For an epidemic with an R0 value of 1.5, the combination of all four social distancing	A modelling study is always a simplification of the reality.

	approximately 30,000		were simulated: school closure, workplace non-attendance, community contact reduction and case isolation.	measures could reduce the final attack rate from 33% to 9% if introduced within 6 weeks from the introduction of the index case. If applied preemptively, anticipating the arrival of the index case into the otherwise uninfected community, this combination of measures reduces the total attack rate to 1.6%, with a correspondingly significant reduction in attendant mortality rates. In contrast, for an epidemic with an R0 value of 2.5 the combination of all intervention measures must be introduced within 2 weeks of the index case to prevent an epidemic developing; delays of 2, 3 and 4 weeks resulted in final attack rates of 7%, 21% and 45% respectively. For an epidemic with an R0 of 3.5, perhaps considered to be a worst-case scenario, our results indicate that the combination of all interventions was unable to reduce the final illness attack rate to less than 10% and unable to prevent an epidemic occurring. However, the rapid activation of measures may significantly arrest epidemic development, giving final attack rates of 16%, 19% and 35% if activated preemptively or with a 1 or 2 week delay, respectively. A similar effect of intervention delay on peak daily attack rates was found.	
Jones et al. 2013, Chicago USA (13)	Simulation of general population	Disease transmission	Comparing effectiveness of	The hygiene intervention applied singly results in fewer infections and lower *R0* than	Significant simplifications in used models.

		model for influenza	hygiene intervention and social distancing in influenza transmission by using 2 disease transmission models.	the social distancing intervention applied singly. Hygiene intervention yields fewer infections for a given level of compliance than the social distancing. Model 1: R0 without interventions: 1,36 R0 with hygiene only: 1,02 R0 social distancing only: 1,16 R0 both interventions: 0,87 Model 2: R0 without interventions: 1,36 R0 with hygiene only: 1,03 R0 social distancing only: 1,15 R0 both interventions: 0,86	

Conclusion – clinical bottom line

Based on the included studies (mainly on influenza), social distancing should be implemented as soon as possible after the announcement of the first case in a country. The success of this intervention decreases if it is not implemented immediately (For a R0=2.5; delays of 2, 3 and 4 weeks resulted in final attack rates of 7%, 21% and 45% respectively) and, according to another study, would barely have any effect after 3 weeks. The effect of social distancing also depends on the epidemiological nature of the virus; since the R0 of COVID-19 is higher than the one of influenza, social distancing will have a smaller effect. Social distancing should be combined with other preventive measures such as hand hygiene and should be maintained for a sufficient period of time; one study even suggested a detrimental effect on viral spread if social distancing was ceased too early.

Comment

The conclusion is mainly based on evidence from model studies on influenza, which is inherently a simplification of the reality. Some model studies are simulated with real data, others are fully computer simulated. There is a need for further epidemiological research.

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