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Randomised controlled trials in medical crisis

Henrik Ullum, CEO, Professor

MISSION

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We prevent and fight infectious and congenital diseases through research, monitoring, diagnostics, and guidance.

PARADIGM SHIFT IN REAL-TIME DATA

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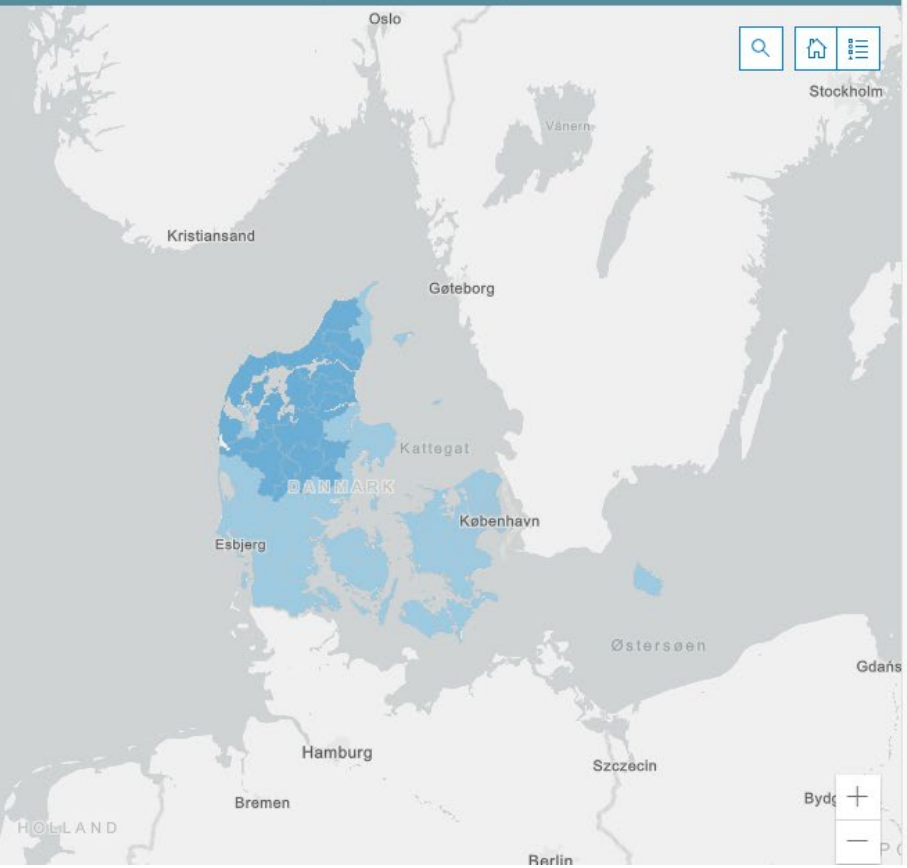
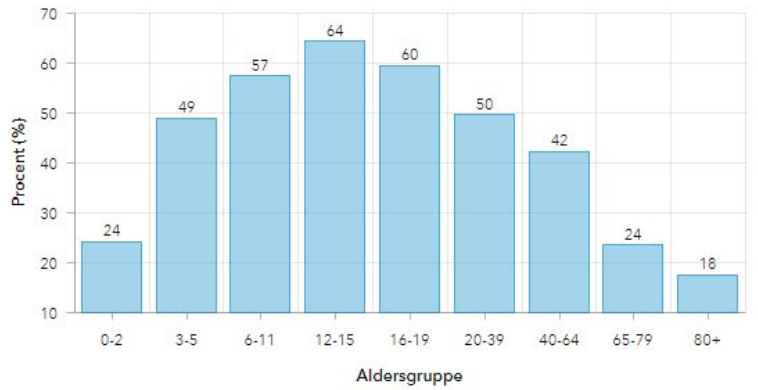
Opgørelser over andele af befolkningen - fra d. 17. december 2021

Smittede	3. stik	Smittede og 3. stik	Smittede og/eller 3. stik
42 %	62 %	23 %	86 %

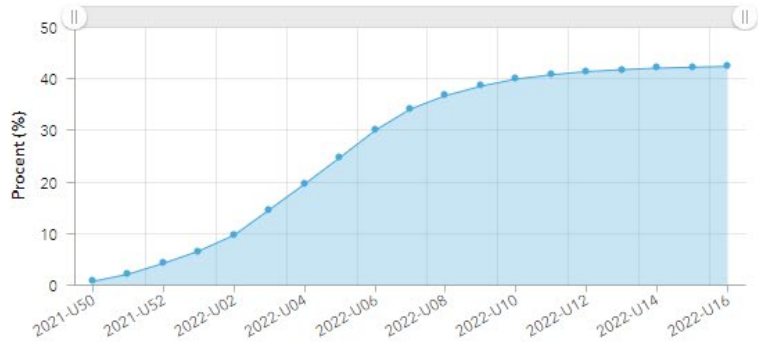
Sidst opdateret: 25. april 2022



Andel smittede pr. aldersgruppe i alle kommuner



Andel smittede pr. uge i alle kommuner for alle aldersgrupper



Many NPI's were used in Denmark

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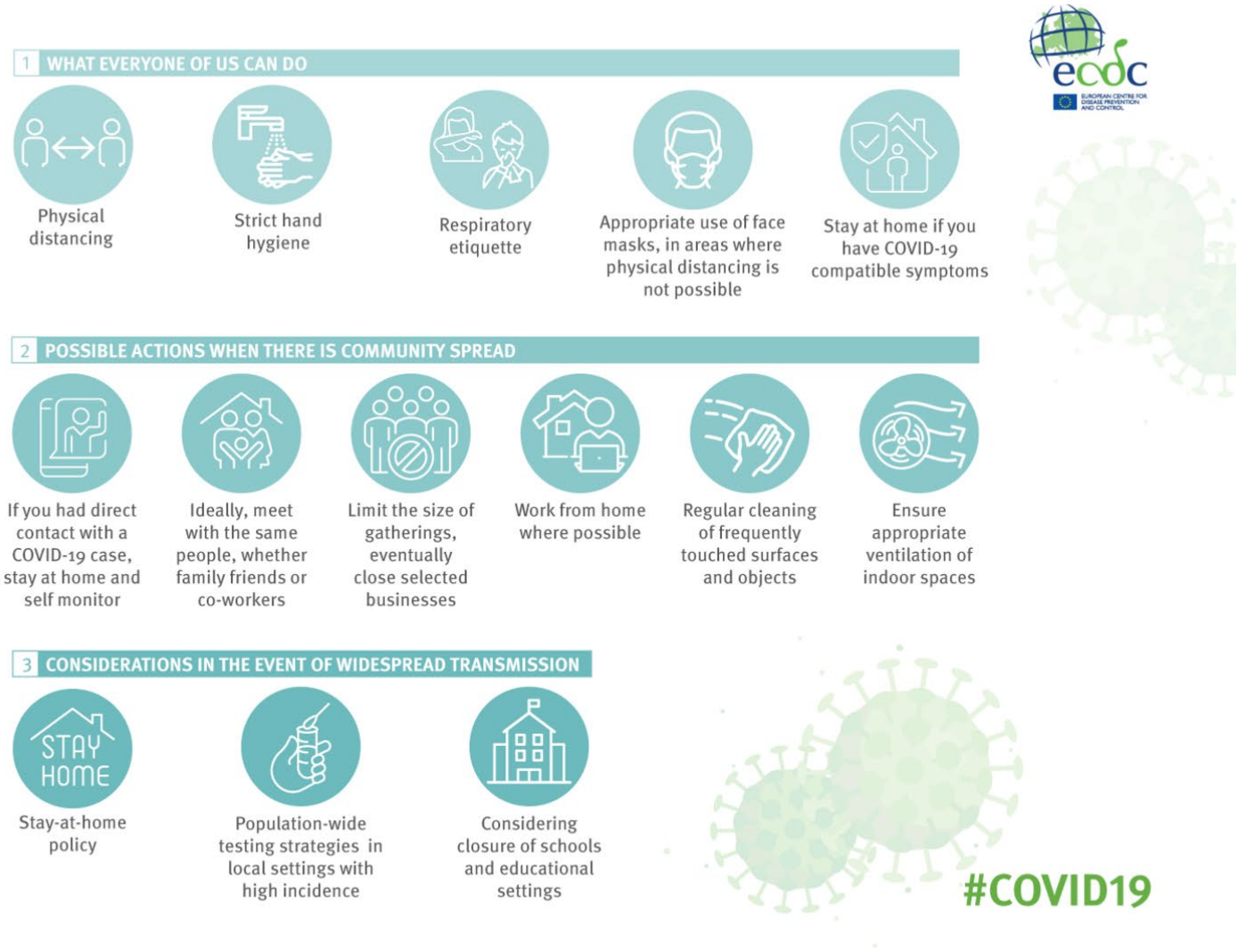
COVID-19

Non-pharmaceutical interventions (NPI) are actions that people and communities can take to help slowing down the spread of viruses such as SARS-CoV-2. Such community mitigation strategies, ranging from individual actions such as regularly practising good hand hygiene to more restrictive measures like limiting size of gatherings, should ideally be implemented in combination and applied at the same time.

The mix of chosen NPI should differ based on the local transmission situation.

It can take several weeks before any implemented NPI might show an effect.

More on NPI and how to apply them: http://bit.ly/COVID19_NPIs



DANMASK: Does mask wearing protect against COVID-19?

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Spring 2020:

- Expected continuous wave of SARS-CoV-2
- Need for rational NPI´s

Masks

- No tradition or recommendations to wear masks in public spaces in Denmark
- Expected large Danish COVID-19 wave
- Need for more evidence

People wear masks on a street in Hong Kong, Friday, Jan. 24, 2020 to celebrate the Lunar New Year which marks the Year of the Rat in the Chinese zodiac. | Source: AP Photo / Kin Cheung(KALB)

Challenges Randomised Controlled Trial (RCT)

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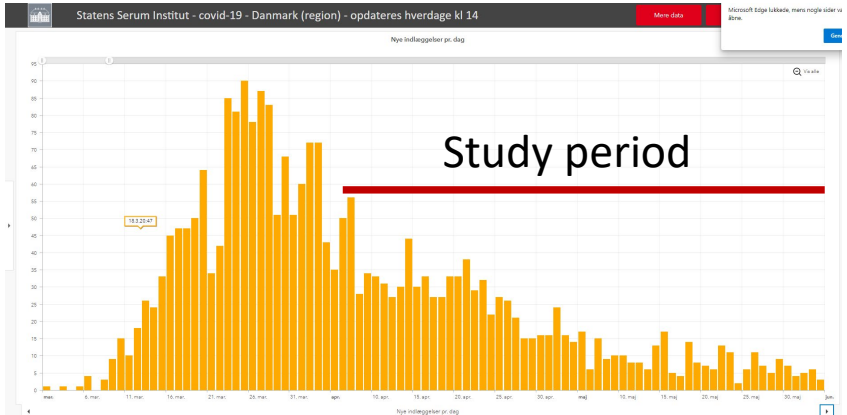
Design

- Funding: need for quick decision
- Staff: great support
- Equipment: lack of masks (delay) and sampling- + testing equipment
- Study size versus power
- Study endpoints: serology
- Not studied: Source control
- Authority approvals: Ethics - Data Protection

Execution

- Participant recruitment/information
- Good Danish control with the epidemic



Study design

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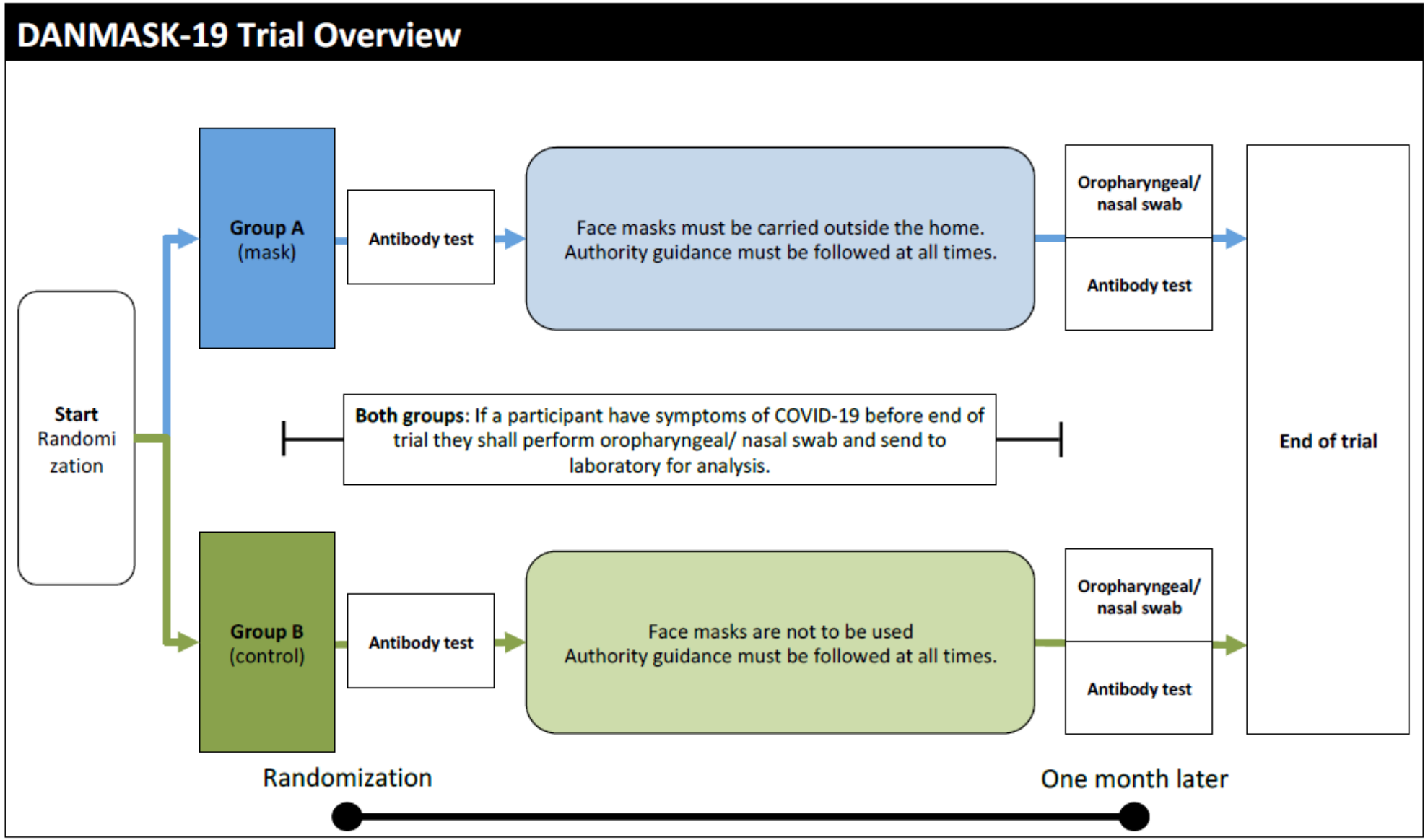

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Annals of Internal Medicine

ORIGINAL RESEARCH

Effectiveness of Adding a Mask Recommendation to Other Public Health Measures to Prevent SARS-CoV-2 Infection in Danish Mask Wearers

A Randomized Controlled Trial

Henning Bundgaard, DMSc; Johan Skov Bundgaard, BSc; Daniel Emil Tadeusz Raaschou-Pedersen, BSc; Christian von Buchwald, DMSc; Tobias Todsen, MD; Jakob Boesgaard Norsk, MD; Mia M. Pries-Heje, MD; Christoffer Rasmus Vissing, MD; Pernille B. Nielsen, MD; Ulrik C. Winsløw, MD; Kamille Fogh, MD; Rasmus Hasselbalch, MD; Jonas H. Kristensen, MD; Anna Ringgaard, PhD; Mikkel Porsborg Andersen, PhD; Nicole Bakkegård Goecke, PhD; Ramona Trebbien, PhD; Kerstin Skovgaard, PhD; Thomas Benfield, DMSc; Henrik Ullum, PhD; Christian Torp-Pedersen, DMSc; and Kasper Iversen, DMSc

Primary Funding Source: The Salling Foundations.

Ann Intern Med. 2020. doi:10.7326/M20-6817 **Annals.org**
For author, article, and disclosure information, see end of text.
This article was published at Annals.org on 18 November 2020.

Results

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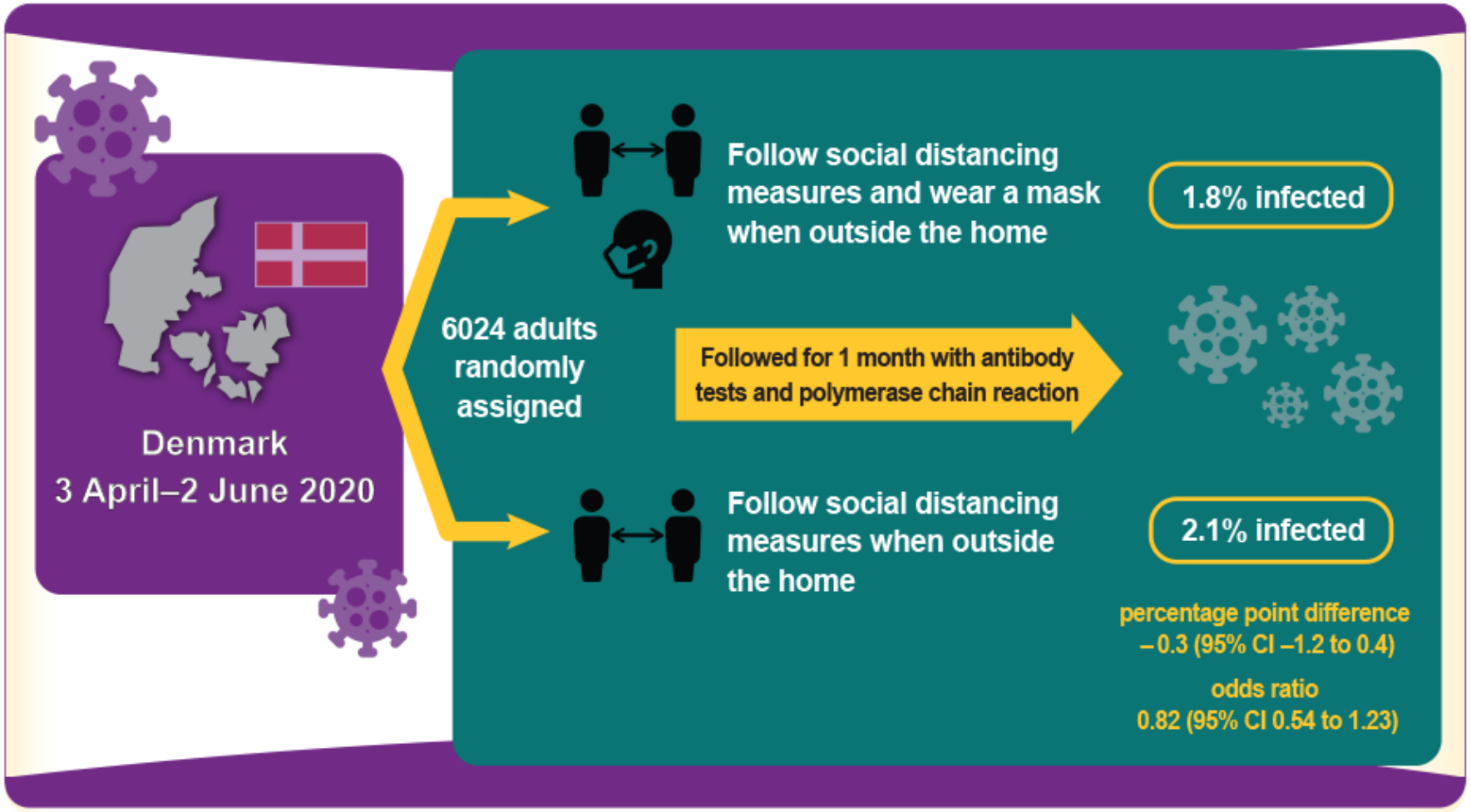
Does a recommendation to wear a surgical mask when outside the home reduce the wearer's risk for SARS-CoV-2 infection in a setting where masks were uncommon and not among recommended public health measures?



SoMe and public media storm

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- Submitted to high impact medical journals = usual delay
- Question: When will the DANMASK study be published
- Problematic answer: The study will be published when there is a journal that is brave enough….”
- Bad timing…
- Strong pressure to release to preprint server – (risk of more controversy)

A lot of criticism and discussion

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ɜER 2020 Jyllands-Posten LOG IND

20.11.2020 KL. 15:01

Masker virker – dansk studie er noget sjusk

Al forskning peger på, at den altovervejende effekt af maskebrug er på udåndingen. Alligevel tester det danske studie på indåndingen. Studiet viser ingenting. Derfor er seks millioner kroner spildt, og resultaterne misforstås ret bredt af presse og offentlighed og bruges som argument imod masker.

Ingen tør åbenbart sige, at studiet er ringe. Måske fordi der står flere professorer og doktorer som afsendere. Det får lov at hænge i luften, at vi ikke har kunnet vise, at masker virker, men ikke, at det skyldes dårligt designet forskning. Tegning: Rasmus Sand Høyer.

Passengers ride a subway in Denmark, where an inconclusive trial on mask wearing took place.

COVID-19

Poor trials of health steps are worse than none, scientists say

Others say small COVID-19 studies accumulate into a clear picture over time

One single study rarely answers all questions

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Lead Researcher Behind Controversial Danish Study Says You Should Still Wear A Mask

Leah Rosenbaum Forbes Staff
Innovation
I write about the business of healthcare.

Updated Nov 18, 2020, 06:25pm EST

TOPLINE A Covid-19 study conducted in Denmark and published in *Annals of Internal Medicine* created a heated discourse on social media as some claimed that the study showed masks were ineffective at preventing Covid-19 transmission, while health experts--including the lead researcher behind the study--disagreed.

Another example

Electronic nudges to increase influenza vaccination uptake in Denmark: a nationwide, pragmatic, registry-based, randomised implementation trial

Niklas Dyrby Johansen, Muthiah Vaduganathan, Ankeet S Bhatt, Simin Gharib Lee, Daniel Modin, Brian L Claggett, Erica L Dueger, Sandrine I Samson, Matthew M Loiacono, Lars Køber, Scott D Solomon, Pradeesh Sivapalan, Jens Ulrik Stæhr Jensen, Cyril Jean-Marie Martel, Palle Valentiner-Branth, Tyra Grove Krause, Tor Biering-Sørensen

Summary

Background Influenza vaccination rates remain suboptimal despite effectiveness in preventing influenza infection and related complications. We investigated whether behavioural nudges, delivered via a governmental electronic letter system, would increase influenza vaccination uptake among older adults in Denmark.

Methods We did a nationwide, pragmatic, registry-based, cluster-randomised implementation trial during the 2022–23 influenza season in Denmark. All Danish citizens aged 65 years or older or turning 65 years by Jan 15, 2023 were included. We excluded individuals living in nursing homes and individuals who had an exemption from the Danish mandatory governmental electronic letter system. Households were randomly assigned (9:1:1:1:1:1:1:1:1:1) to usual care or nine different electronic letters designed on the basis of different behavioural nudging concepts. Data were sourced from nationwide Danish administrative health registries. The primary endpoint was receipt of influenza vaccination on or before Jan 1, 2023. The primary analysis assessed an analytical set of one randomly selected individual per household, and a sensitivity analysis included all randomly assigned individuals and accounted for within-household correlation. The trial is registered with ClinicalTrials.gov, NCT05542004.

Findings We identified 1 232 938 individuals aged 65 years or older in Denmark and excluded 56 436 (4·6%) individuals living in nursing homes and 211 632 (17·2%) with an exemption from the electronic letter system. We randomly assigned 964 870 (78·3%) participants across 691 820 households. Compared with usual care, influenza vaccination rates were higher in the group receiving an electronic letter highlighting potential cardiovascular benefits of vaccination (81·00% *vs* 80·12%; difference 0·89 percentage points [99·55% CI 0·29–1·48]; p<0·0001) and the group receiving repeated letters at randomisation and at day 14 (80·85% *vs* 80·12%; difference 0·73 percentage points [0·13–1·34]; p=0·0006). These strategies improved vaccination rates across major subgroups including those with and without established cardiovascular disease. The cardiovascular gain-framed letter was particularly effective among participants who had not been vaccinated for influenza in the previous season ($p_{interaction}$=0·0002). A sensitivity analysis of all randomly assigned individuals accounting for within-household clustering yielded similar findings.

Interpretation Electronically delivered letters highlighting potential cardiovascular benefits of influenza vaccination or sent again as a reminder significantly increased vaccination uptake across Denmark. Although the magnitude of effectiveness was modest, the low-touch, inexpensive, and highly scalable nature of these electronic letters might be informative for future public health campaigns.

Funding Sanofi.

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See Online/Comment https://doi.org/10.1016/S0140-6736(23)00453-1

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Compared with usual care, influenza vaccination rates were higher in the group receiving an electronic letter highlighting potential cardiovascular benefits of vaccination (81·00% vs 80·12%; difference 0·89 percentage points [99·55% CI 0·29–1·48]; p<0·0001) and the group receiving repeated letters at randomisation and at day 14 (80·85% vs 80·12%; difference 0·73 percentage points [0·13–1·34]; p=0·0006).

Conclusions

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- Medical history is rich in unjustified interventions
- We need to perform research with clinical relevant endpoints
- Observational data are often biased
- Alternative designs to classical RCT´s may be needed i.e. ventilation & air cleaning
- Medical decisions must be based on the combined evidence and not single studies
- Lack of perfect evidence should not prevent action in acute crisis, but if action is needed - initiatives should be lauched to verify the efficay of the intervention
- Acuteness should not change general scientific or clinical methods

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Thanks for listening