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# CJIC

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Revue canadienne de prévention des infections

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## INSIDE



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Pathogens
are always
evolving.
So are we.
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The COVID-19 pandemic demands the best in infection control

# Stop the Spread of All Infectious Diseases

Vernacare's single-use Human Waste Disposal System can help reduce the spread of all infectious diseases including COVID-19 and C. difficile.

Hospitals across Canada have converted from Bedpan Washers to Vernacare's environmentally friendly and cost-effective human waste management system.

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- Single-use patient wipes that are maceratable for safe and easy disposal

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# Clorox® innovation meets disinfection challenges

The Clorox Company knows cleaning and disinfection. We apply this thinking to not only new and effective chemistries, but also revolutionary new application methods for efficient and effective disinfection. This innovation can help as we adjust to the "new normal" of clean needed in the wake of the COVID-19 pandemic.

Despite the best efforts, manual cleaning and disinfection methods can miss areas, leaving bacteria and viruses on hard-to-reach surfaces. In fact, only about 50% of surfaces in hospital rooms are effectively disinfected.[1] But electrostatic spraying technology, a new method for surface disinfection, can help address this.

## Electrostatic spray technology

Electrostatic spray technology is an established technology with exciting new application in surface disinfection.

With electrostatic sprayers, an electrode introduces an attractive charge, which atomizes the disinfecting solution. The charged particles are attracted to surfaces and "wrap around" the surfaces, resulting in uniformly coated surfaces.

## Electrostatic vs. trigger spray vs. mister/fogger

With trigger sprays, liquid is unevenly deposited on surfaces, which requires wiping and incomplete coverage of hard-to-reach surfaces.

Misters passively deposit uncharged liquids on surfaces, require any vents in the area being treated to be sealed, and have long re-entry times after use.

Electrostatic sprayers on the other hand, actively deposit charged liquids on surfaces, ensuring wraparound coverage, with no need to seal the vents in the area being treated, and no time required before re-entry.

## How to choose electrostatic technology

When making the move to electrostatic technology, some things to consider are the design of the system, the chemistry of the products intended for use with the electrostatic sprayer, and safety. Think about:

**Cord or Cordless?**
With a corded electrostatic sprayer, there is consistent droplet charge and uniform surface coverage, resulting in a good wrap around objects and ensuring proper coverage of the front, sides and back of surfaces. In contrast, while cordless sprayers have the advantage of mobility, this comes at a price: a battery-powered sprayer can have inconsistent droplet charge, uneven surface coverage and a poor surface wrap, not to mention the time and expense of battery charging, maintenance and replacement.

Some additional factors to consider include the capacity of the sprayer, the size of the area that can be covered per hour of use or per volume of disinfectant cleaner used, and the ergonomics of the design, which will impact the ease of use.

**Chemistry**
When deciding on a disinfectant cleaner to use with your electrostatic sprayer, it is important to choose trusted solutions that are Health Canada-approved for use through the sprayer.

Some other factors to consider include: the active ingredients, if it is a one-step or multi-step formulation, if the product is ready-to-use or requires dilution, whether the formula has low odour and residue, contact time required to kill common pathogens, and number of pathogens the disinfectant cleaner is proven to kill.

**Safety**
Consider operator safety and determine both Personal Protective Equipment (PPE) requirements and re-entry time of the disinfectant cleaners used with the electrostatic sprayer.

Electrical safety is an important consideration, and both the device and components such as batteries should be tested and certified. Ensure that your electrostatic sprayer has been tested by a Nationally Recognized Testing Laboratory (NRTL) such as Underwriters Laboratories (UL) or Electrical Testing Laboratories (ETL).

**Electrostatic spraying is more than a device – it's a system**

Find out more about Electrostatic Spray Technology and how it can be used in applying surface disinfectants. Scan the QR code to watch the Infection Prevention and Control (IPAC) Canada webinar Electrostatic Technology: A New Method for Surface Disinfection, presented by Dr. Katherine Velez, Senior Scientist at CloroxPro™.

## Is the disinfectant you're using with your electrostatic sprayer compliant with Health Canada regulations?

The latest information from Health Canada regarding disinfectants applied via Electrostatic Sprayers indicates that the products used must be approved by Health Canada (i.e., have a DIN), and the Direction of Use (DFU) on the master label must state "Electrostatic Sprayer" (ES) as a method of disinfection to be compliant.

The Clorox® electrostatic sprayers, the Clorox Total 360® System and Clorox Total 360® ProPack system (corded backpack), exclusively use Clorox® products for superior coverage of surfaces with trusted solutions.

## Approved for use with electrostatic sprayer:

- **Clorox Total 360® Disinfectant Cleaner** (DIN 02460769)
- **Clorox Healthcare® Spore Defense™ Cleaner Disinfectant** (DIN 02494663)
- **Clorox® Anywhere® Daily Sanitizer & Disinfectant** (DIN 02495716)

Only Clorox Total 360®, Spore Defense™ and Anywhere® meet the Health Canada designation for use with an electrostatic sprayer.

**Learn more at CloroxPro.ca | healthcare@clorox.com**

CLOROXPRO™

**References: 1.** Bhalla A, *et al.* Acquisition of Nosocomial Pathogens on Hands After Contact With Environmental Surfaces Near Hospitalized Patients. *Infect. Control Hosp. Epidemiol.* 2004;25(2):162-4. **2.** Velez K. Electrostatic technology: A new method for surface disinfection. CloroxPro Canada 2020. **3.** Velez K. Evaluating Electrostatic Sprayers for Surface Disinfection. CloroxPro Canada. 2020. **4.** CloroxPro Canada. Data on file. Dec 18, 2020. [Health Canada response to S. Coombs]. **5.** CloroxPro Canada. Clorox Total 360® System. https://www.cloroxpro.ca/products/clorox/total-360/. Accessed January 5, 2021.

# The invisible guardian.


## Everyday sporicidal protection available for the Clorox Total 360® System.

CloroxPro™ offers the powerful Spore Defense™ formulation, exclusively for the Clorox Total 360® System.

- Health Canada-approved (DIN: 02494663)
- Kills SARS-CoV-2 (the virus that causes COVID-19), plus 42 other pathogens in just 1 minute, including MRSA, VRE, measles & polio
- Also kills *C. difficile* in 5 minutes
- 0.25% sodium hypochlorite formula has a low odour, low residue formula, with high surface compatibility
- Requires no Personal Protective Equipment (PPE) and zero re-entry time

Clorox Total 360® System with Spore Defense™, when used regularly, provides your facility with invisible yet effective outbreak prevention.

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CLOROX TOTAL 360

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# PCS TORAYSEE™ PROGRAM FOR HEALTH CARE

**Toraysee™ cloth a proven technology with years of successful use currently used in greater than 1000 health care facilities and clinics in Japan**

Toraysee™ cloth a single cloth can be used all day to repeatedly clean and disinfect frequently touched surfaces and equipment.

Toraysee™ is a cloth that specializes in the removal of organic materials and other dirt and washing without the use of chemicals.

In the cleaning of medical equipment and instruments, priority is given to the "washing" process (removal of organic materials and dirt).

## PCS INTRODUCTION OF TORAYSEE™ DAMP CLEANING PROCESS INTO OUR HEALTH CARE PROGRAM HAS MANY BENEFITS

- Synergistic cleaning and disinfecting with PCS 5000 Oxidizing Disinfectant Cleaner
- Reduced chemical damage to sensitive equipment
- Safer method of using potent sporicidal disinfectants

**Reduced impact on the environment. One Toraysee™ cloth can prevent the wasteful discharge of thousands of single use pre- moistened wipes.**

## MICROBIAL-CONTROL TREATMENT PROVIDES HYGIENE AND PEACE OF MIND

**What is microbial-control treatment?**

Microbial-control treatment is a treatment that aims to control microbial growth on the cloth's fibres.

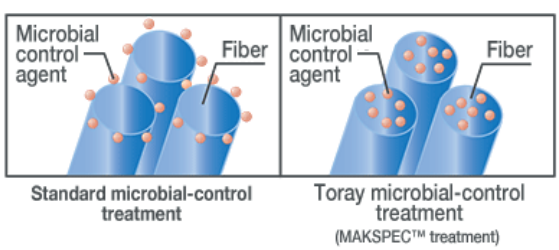
### Microbes targeted by microbial-control treatment

Test method: JIS L 1902 Liquid culture absorption method

| Tested microbes | Specific applications |
|---|---|
| Staphylococcus aureus | ○ |
| Klebsiella pneumoniae | ○ |
| Methicillin-resistant Staphylococcus aureus | ○ |

⊠ Evaluation criteria: Antibacterial activity value > Control cloth multiplication value
＊Comparison between antibacterial/antifouling value and control cloth multiplication value

### Mechanism of microbial-control treatment




Compared to ordinary treatment, in which the microbial-control agent adheres to the outside of the fibers, with Toray's microbial-control treatment (Makspec®), the microbial-control agent infiltrates the fibers, thus sustaining the microbial-control effect.

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# TORAYSEE™ PCS 5000 OXIDIZING DISINFECTANT CLEANING PROCESS AND COST OF USING ONE TORAYSEE™ PER DAY.


## PROCESS

### Materials

- Small oblong or square container with lid
- 250 mls of PCS 5000 Oxidizing Disinfectant/Disinfectant Cleaner
- Toraysee™ cloth
- Bucket with rinse water

## PROCEDURE

- Add 250 mls of PCS 5000 to container add Toraysee™ cloth and check lid is secure, ensure container has work place label

### To clean and disinfect with Toraysee™ cloth

- Remove lid from container
- Squeeze out liquid from Toraysee™ cloth
- Wipe over surfaces with damp Toraysee™ cloth

### How to reuse

- Rinse cloth with water squeeze out liquid
- Replace cloth in PCS 5000 Oxidizing Disinfectant Cleaner
- PCS 5000 Oxidizing Disinfectant Solution disinfects Toraysee™ and saturates cloth for next use

### To clean delicate or chemically sensitive surfaces

- Remove Toraysee™ from PCS 5000 Disinfectant solution
- Squeeze out liquid
- Rinse cloth in water and squeeze out liquid from cloth
- Wipe delicate surfaces or equipment with damp Toraysee™

These processes can be used for prolonged periods of time but common practice is to rinse Toraysee™ cloth at the end of use for the day, empty and rinse the container. Water Rinse Toraysee™ after use for the day squeeze excess liquid from cloth and allow to air dry.

- Toraysee™ Antimicrobial finishing process has proven to discourage microbial growth on fibres even after 60 hospital laundering cycles.

- Dampened with water only Toraysee™ has demonstrated the ability to remove greater amounts of ATP, bacteria and viruses than pre-moistened disinfectant wipes and split microfibre cloths.

- Toraysee™ after soaking in 1 % sodium hypochlorite for 5 weeks removed 99.6% of soil as compared to 99.5% before treatment. Demonstrating Toraysee™ maintained excellent removal of organic soils even with prolonged pre sence of strong concentrations of sodium hypochlorite.

| **Cost of use** Based on 50 use applications per day. Toraysee cloth cost based on sixty days of use. | | |
|---|---|---|
| Cost per day | = | .20 |
| Number of cloths used for sixty days | = | 1 |
| PCS 5000 use per day 250 mls | = | .74 |
| **Toraysee™ / PCS 5000 cost per day** | **=** | **.94** |
| **Cost per day 5990 • 50 12”x12” wipes per day** | **=** | **22.00** |
| NUMBER OF WIPES USED IN SIXTY DAYS | = | 3000 |
| **Cost per day 5987-6 • 7”x12” wipes per day** | **=** | **12.27** |
| NUMBER OF WIPES USED IN SIXTY DAYS | = | 3000 |
| Bucket saturation of microfibre cloths 3 L | = | 8.88 |
| Cost of microfibre cloths 50 required launder cost + Cost of cloths | = | 8.34 |
| Number of cloths used sixty days | = | 50 |
| **Split microfibre charged bucket system cost per day** | **=** | **17.22** |

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Bringing Science to the Art of Cleaning®

# PCS 5000 OXIDIZING DISINFECTANT/DISINFECTANT CLEANER


- Active ingredient sodium hypochlorite 0.5%
- Available in Canada only **DIN: 02360500**
- Hospital grade disinfectants with a 5 minute contact time to disinfect C.difficile spores
- PCS 5000 solution containing a blend of natural ingredients
- Purified water, Sodium chloride, Carbonates, sodium hypochlorite and sodium hydroxide as PH adjuster
- Contains no detergent surfactants, masking fragrances, silicates or other synthetic chemicals
- Buffered stable formulations with a three year shelf life.
- Sodium hypochlorite normally deteriorates rapidly with shelf life from date of manufacture of 11 months for some sodium hypochlorite products
- Using PCS 5987-6, 6060-6 or 5990 wiper kits insures wipes have the sodium hypochlorite concentration on the label when put into service
- PCS 5000 Oxidizing Disinfectant/Disinfectant Cleaner equal to 1 and 10 bleach solution recommended by public health officials more than any other disinfectant when outbreaks occur or new pathogens emerge

## Quantitative Carrier Test # 3 (QCT-3):

**The objective of this study was to:** a. Conduct laboratory-based testing on the use of a disinfectant cleaner wipe using PCS 5000 (Sodium Hypochlorite 0.5% w/w) for the microbial decontamination of hard, non-porous environmental surfaces representing those found in healthcare settings. The aim here was to evaluate the efficacy of a cleaning/sanitizing process using a wipe with PCS 5000 cleaner.

### SUMMARY OF RESULTS

**Test Substance:** PCS 5000 Oxidizing Disinfectant Wipe.
Test Carriers 1 cm diameter disks of brushed stainless steel.

**Dilution:** PCS 5000 was tested as Ready-to-Use (RTU), No dilution was required.

**Test Organism:** Mixture of Clostridium difficile spores (ATCC 43598), Staphylococcus aureus (ATCC 6538) and Serratia marcescens (ATCC 13880)

**Exposure Time:** No exposure time was considered. The disks of each platform were transferred to neutralization solution immediately at the end of wiping.

**Exposure Temperature:** Ambient temperature (22±2°C)

**Soil Load:** In accordance with the ASTM standard E2197, a mixture of bovine mucin, bovine serum albumin, and yeast extract was used to give a total protein concentration equal to that in 5% bovine serum in test microbial suspension.

**Neutralizer:** PBST +0.3% Sodium thiosulfate

### TEST SYSTEM

"Wipe" method, starting with the contaminated platform, both platforms were wiped in one step in a pre-determined manner (as instructed by manufacturer). The wiping was performed with one piece of Ready-to-Use Cleaner wipe, started from the contaminated platform back and forth twice to the end of transfer platform.

Constant pressure of 2-3 lbs was applied during wiping process.

A separate platform (transfer platform) was used to determine if, and how much, microbial contamination could be transferred to uncontaminated surfaces in the immediate vicinity.

**Vegetative Bacteria (S. aureus and S. marcescens)**
Average CFU per square centimetre

| | CFU/cm2 | | | Percent | | Average Percent | |
|---|---|---|---|---|---|---|---|
| Product | Control | After Wiping | Transfer | Reduction | Transfer | Reduction | Transfer |
| 5000 Wipe Test 1 | 25,000 | 0 | 0 | 100 | 0 | 100 | 0 |
| 5000 Wipe Test 2 | 25,100 | 0 | 0 | 100 | 0 | | |

**C. difficile spores**
Average CFU per square centimetre

| | CFU/cm2 | | | Percent | | Average Percent | |
|---|---|---|---|---|---|---|---|
| Product | Control | After Wiping | Transfer | Reduction | Transfer | Reduction | Transfer |
| 5000 Wipe Test 1 | 3050 | 0 | 0 | 100 | 0 | 100 | 0.01895 |
| 5000 Wipe Test 2 | 1350 | 0 | 0.51 | 100 | 0.0379 | | |

**The total of three types of micro organisms**
Average CFU per square centimetre

| | CFU/cm2 | | | Percent | | Average Percent | |
|---|---|---|---|---|---|---|---|
| Product | Control | After Wiping | Transfer | Reduction | Transfer | Reduction | Transfer |
| 5000 Wipe Test 1 | 29,000 | 0 | 0 | 100 | 0 | 100 | 0.00097 |
| 5000 Wipe Test 2 | 26,500 | 0 | 0.51 | 100 | 0.00193 | | |

Conclusion using PCS process of supplying the PCS 5000 in kits keeping liquid and wipes separate until activated on site provided a potent moistened wiper that completely removed all of the vegetative bacteria and C.difficile spores with a one wipe process without allowing for a contact time.

" Disinfectant residues should be removed."

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# ABOUT TORAYSEE™

Toraysee™ is a cleaning cloth made using Toray's ultra-fine fibres.

Reusable Toraysee™ cloth a single cloth can be used all day to repeatedly clean and disinfect frequently touched surfaces and equipment.

Toraysee™ cloths are currently used in more than a thousand health care facilities and clinics in Japan.

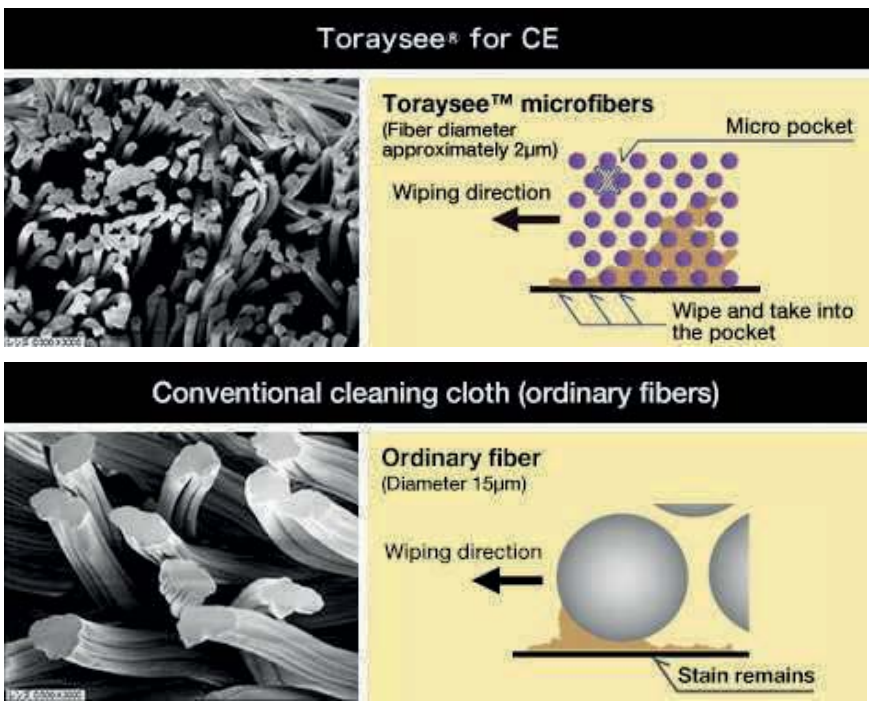
In the cleaning of medical equipment and instruments, priority is given to the "washing" process (removal of organic materials and dirt).

Toraysee™ is a cloth that specializes in the removal of organic materials and other dirt and washing without the use of chemicals.

It can be used wet or dry according to requirements, and can also be impregnated with disinfectant.

## WIPING MECHANISM OF TORAYSEE™

Cleaning the touched surfaces : CONTACT POINT




Toraysee™ has ultra-fine (2 μm) fibres arrayed at high densities. Even if the first fibre were to leave some oil film behind, the next fibres will be sure to pick it up.

The greater fibre density also creates Micro Pockets that act as efficient reservoirs of the wiped contaminant preventing transfer and recontamination of other surfaces.

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Call 435-259-5931

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* Based on third-party testing. 

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# Infection prevention and control in long-term care: Lessons learned from COVID-19 outbreaks and future perspectives

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## EDITORIAL

Long-term care homes (LTCHs) have experienced the brunt of the COVID-19 pandemic [1]. The impact of the disease in LTCHs could be attributed to several factors. Namely, gaps in facility design, inadequate infection prevention and control (IPAC) systems and overall operational challenges. Also, long-term care operators have struggled to balance key aspects of the Resident Bill of Rights and the implementation of appropriate IPAC measures. For example, resident cohorting, restriction of outdoor activities, restriction of visitation, cancellation of group activities and communal dining. These, and other imposed isolation measures on one hand have been salient in mitigating the risk of infection transmission within the home, but on the other hand, have had significant implications in residents' rights and freedom as well as their mental wellbeing. Beside these psychosocial and operational issues, the COVID-19 pandemic has also exposed gaps in critical aspects of long-term care, which require attention in order for LTCHs to be able to appropriately manage future pandemic threats [2]. The shared accommodation settings in many LTCHs facilitate the transmission of infections among residents who are vulnerable owing to their advanced age and with often underlying medical conditions such as diabetes, chronic respiratory, cardiovascular and cerebrovascular diseases, malignancy, and functional decline (dementia). Also, people living with dementia have high risks of contracting an infection during an outbreak due to reduced cognitive ability to adhere to IPAC measures [3]. In this editorial, I will discuss some of these challenges, and provide a focus for future control efforts, based on evidence and experience from the response of several outbreaks.

*First, most LTCHs are not designed to deal with outbreaks of pandemic potential*. Adequate ventilation is important to reduce the transmission of infections in LTCHs especially those transmitted by airborne and droplet means [4]. A well-ventilated system can reduce the risk of airborne infection transmission in indoor spaces by diluting the concentration of potentially infectious aerosols through ventilation with outside air. Ideally, the HVAC system in LTCHs should be inspected, maintained and regularly cleaned [5]. According to the World Health Organization (WHO), in the absence of aerosol-generating medical procedures (AGMPs), adequate ventilation is considered to be 60 litres/second per resident (L/s/resident) for naturally ventilated areas or six air changes per hour (ACH). In rooms where AGMPs are performed, specific requirements should be met. Homes using natural ventilation systems should ensure that contaminated air exhaust is piped directly outdoors, away from air-intake vents, clinical areas and people. The recommended average natural ventilation rate is 160 L/s/patient [5]. In facilities where a mechanical ventilation system is available, negative pressure should be created to control the direction of airflow. The ventilation rate should be between 6-12 ACH with a negative pressure differential of ≥2.5 Pa (0.01-inch water gauge) to ensure that air flows from the corridor into the resident room [6]. Beside the negative air pressure system, temperature/humidity controls and the use of UV-C light disinfection systems are attractive interventions to improve the overall environment of care for residents. Also, considering the fact that most infections are transmitted by contact means, emphasis should be placed on reducing the number of touch points in LTCHs. For example, touchless faucets, touchless bathroom doors, touchless wall-mounted alcohol-based hand rub or soap dispensers, touchless paper towel dispensers, touchless foot-operated waste bins, etc.

Additionally, breaking the chain of transmission of infection between residents, will require the provision of more single rooms with dedicated bathrooms against double or ward rooms. Each end of the resident home area (RHA) should have a separate entrance and a separate dining room, activity room, lounge, shower/tub room and bathroom to support cohorting by home area. Corridors in RHAs should have a minimum width of 2.4 metres to facilitate the easy transfer of beds during resident movement (cohorting). An increased corridor space may also support physical distancing and ease the movement of carts within the unit [7]. There should be additional vacant rooms to support isolation of cases and space to create quarantine zones.

*Second, a significant challenge in managing COVID-19 outbreaks in LTCHs is the ability to restrict or isolate residents with cognitive impairment, or those who wander throughout the home.* Residents who, because of cognitive decline, are unable to adhere to self-isolation measures and other IPAC precautions contribute significantly to the spread of the virus within the home. During wave one, an increase in the prescription of psychoactive medications to residents occurred as a means to prevent wandering and support self-isolation. Later on, non-pharmacological interventions were increasingly seen to be valuable and helpful to distract residents with dementia and keep them in their rooms. Examples include:

(1) engaging the residents in meaningful activities based on the resident's interest, e.g., playing favourite music, television show, or a movie in their own room;
(2) creating an activity kit based on the resident's interests (e.g. photo album, magazines, picture books, puzzles, math sheets, etc.);
(3) facilitating phone/video calls with family and friends, or playing pre-recorded messages;
(4) making the resident's room as comfortable and appealing as possible, e.g., displaying pictures of family on the walls and/or pieces of their life story (e.g. pictures of places or items of significance);
(5) establishing and promoting a daily routine and exercise;
(6) regularly attending to their demands and physical needs [8].

Although essential in outbreak control, there were significant challenges in achieving this. Homes are, therefore encouraged to train more activity aides on behavioural knowledge and skills to engage residents in a meaningful way in their rooms. An effective implementation of these strategies may eliminate the need for unnecessary pharmacological intervention. However, during periods when the resident is unwilling to stay in his or her room, other strategies such as staffing for one-to-one care, encouraging frequent hand hygiene, and encouraging the resident to wear a mask, if tolerated, may reduce the risk of transmission.

*Third, is the consideration for paid sick leave for LTCH employees.* Although all employees are routinely screened for symptoms of COVID-19, it has been suggested that because of fear of work exclusion and unpaid sick days, some LTCH employees have failed to declare mild symptoms during entry screening. In some cases, these employees have been deemed to have worked while positive as was determined by subsequent surveillance testing and contact tracing by the local public health units. It is essential, therefore, for all LTCHs to implement sick leave policies that are non-punitive, flexible, and consistent with public health policies that encourage employees to stay home when ill [9]. Providing paid sick leave will increase the rate of staff presenting voluntarily for testing and isolating if they have symptoms, ultimately reducing the risk of transmission to residents and staff within the home [5].

*Fourth, essential visitors to LTCHs have also been implicated in some cases as the source of outbreaks within the home.* Efforts should be made to protect residents in LTCHs by implementing a controlled visitation policy. Beside active screening of visitors and regular testing, a standard operating procedure allowing visits to LTCHs should build on the existence and continuous reinforcement of a strong IPAC policy in the home [5]. Visitors should be required to demonstrate full understanding of basic IPAC expectations especially related to hand hygiene compliance, the appropriate use of personal protective equipment (PPE) and the requirement of physical distancing. As a matter of fact, essential visitors need to be held at a comparable standard of infection prevention and control as employees as the risk of infection is the same. They should take a mandatory IPAC training prior to being designated as an essential caregiver or essential visitor.

*Fifth and most important is an infection prevention and control program*. Each LTCH should have an IPAC program and assign an individual with the required training in IPAC to be the lead [10]. This individual will be responsible for a wide range of activities, including developing IPAC policies and procedures, performing healthcare-associated infection surveillance, providing IPAC training to employees, and coordinating IPAC audits. Ideally, each LTCH that has more than 100 residents should have an IPAC specialist certified in infection control (CIC®). The IPAC focal person in the LTCH should work closely with relevant provincial and local public health authorities to facilitate the roll out of directives. Some long-term care operators have gone the extra mile to hire epidemiologists and this has really made a difference in their COVID-19 outbreak response efforts. Typically, healthcare epidemiologists will look at the distribution (frequency, pattern) and determinants (causes, risk factors) of the disease within the home, community, or the general population and search for transmission routes, trends, and identify people who are at risk, as well as determine how to control or stop the spread, or prevent it from happening again.

It is essential that all long-term care employees complete a mandatory IPAC education on hire and annually thereafter. Once an outbreak is declared, there should be a mandatory IPAC education refresher for all employees on core IPAC expectations such as transmission-based precautions, hand hygiene, proper techniques of PPE donning and doffing, and environmental cleaning and disinfection. Also, facility IPAC assessments by a regulatory or qualified independent agency should occur at least twice a year and immediately after a home goes into outbreak to ensure that appropriate containment mechanisms are in place. The home must develop a corrective action plan after each assessment, and

be accountable to ensure that all deficiencies are addressed in a timely manner.

Also, it should be mentioned that infection prevention and control audits are a key component of the IPAC program and this should include auditing of critical practice areas such as hand hygiene compliance, effective PPE donning and doffing practices, and environmental cleaning and disinfection efficiency and effectiveness. Additionally, to protect residents from infections that are potentially transmitted by droplet means, it is essential to introduce both breakroom and smoking areas audits in order to ensure physical distancing, as these are the areas where staff are most likely to be without the required PPE (e.g. masks). The target for these audits has to be set by each LTCH and the home must be accountable to meet the target. During the course of the COVID-19 pandemic, some homes in Ontario, Canada, have set a daily target by using the formula: resident census divided by 3. For example, if the number of residents in the home is 90, the daily hand hygiene target is 30 observations. A good strategy to meet this audit target is the implementation of IPAC champions (employees within the home who have a knack for infection prevention and control) who will be responsible to audit, educate and serve as change agents in order to overcome resistance and improve IPAC compliance among staff. Ideally, the composition of the IPAC champions should be 8% of staff census and should consist of employees from any department who can serve as role models to their colleagues.

It is also essential to encourage and support residents and visitors to perform hand hygiene as required, in particular when hands are soiled, before and after meals, or after coming into contact with high-touch surfaces. The implementation of both the Fluorescent gel assessment (Glo Germ) and the ATP (Adenosine Triphosphate) cleaning and disinfection audit may also ensure a safer environment for residents and staff. The fluorescent markers are designed to assess environmental cleanliness, i.e. the physical removal of debris from surfaces. On the other hand, the quantitative ATP bioluminescence enables measurement of bioburden and provides an assessment of the disinfection efficiency [11]. Combining the two audit tools will undoubtedly improve the overall environmental cleaning and disinfection quality initiative of the home.

*Finally, the way in which an outbreak response is conducted will reflect the outcome.* A system that has been shown to produce favourable results is a multisectoral integrated outbreak management team where partners from across different agencies come together to coordinate outbreak management in a LTCH. This multisectoral outbreak management system has been shown to improve accountability by the licensee leading to better outcomes. For example, in Ontario, Canada, the multisectoral outbreak management team consists of Public Health Ontario (PHO), the local Health Unit (HU), the Local Health Integration Network (LHIN), the Ministry of Long-Term Care (MLTC), the Ministry of Health (MOH), a local hospital partner and the LTCH. Each of these agencies comes to the table with a unique perspective and accountability requirement. PHO, e.g., offers laboratory support (i.e., testing and typing of specimens during an outbreak) and creates guidance and best-practice resources; the HU takes the lead on enforcing actions that protect and promote the health of the population and contribute to reducing health inequities. The LHIN, following its mandate as a Crown Agency ensures access to high-quality health services, coordination of effective and efficient management and mobilization of resources to support the home. The hospital partner provides support with the management of high-acuity residents and facilitating the turnaround time of laboratory results [12]. The MLTC takes the lead in setting priorities to protect the health of the residents through the application of legislation, regulations, standards, policies and directives to support strategic goals to improve care of the residents, and strengthening overall healthcare delivery. The LTCH, as the licensee, is accountable to all these agencies and ensures resident safety and quality of care is a priority that should be met.

## CONCLUSION

Together, a lot has been learned with regards to the COVID-19 pandemic that has lasted for over a year (and counting). The time to change the paradigm of care in long-term care is now. Each nation owes its residents in LTCHs the right to protect them against current and future pandemic threats and the first level of change must start with the environment of care followed by the care itself, and all parties need to be accountable in their responsibility in meeting these two essential aspects of resident well-being.

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REPRINT

# Person-to-person transmission of microbes in a nursing home serving patients in a persistent vegetative state

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## ABSTRACT

**Background:** A probable outbreak of respiratory disease in a nursing home serving exclusively patients in a persistent vegetative state (PVS) resulted in hospitalization of eight patients.

**Methods:** Microbes from all PVS patients' respiratory tracks and environments were surveyed by microbiological methods. Major pathogenic microbes were analyzed by pulsed-field gel electrophoresis (PFGE).

**Results:** 24 PVS patients were investigated. Half were colonized with at least four different pathogenic microbes in their respiratory tracts. The most prevalent microbes were *Pseudomonas aeruginosa* in 15 patients (62.5%), *Serratia marcescens* in 14 (58.3%), *Citrobacter koseri* in nine (37.5%), *Streptococcus pneumoniae* in six (25%), and *Proteus mirabilis* in five (20.8%). By PFGE analysis, one major pulsotype each was identified for *S. marcescens* (92.9%, 13/14) and *S. pneumoniae* (100%, 6/6), whereas diverse pulsotypes were identified for *P. aeruginosa*, *C. koseri*, and *P. mirabilis*. Both major pulsotypes for *S. marcescens* and *S. pneumoniae* were also found in strains from patients outside the nursing home. No environmental reservoir was found for prevalent microbes.

**Conclusions:** Clonal transmission of *S. marcescens* and *S. pneumoniae* among PVS patients in the nursing home was evident, indicating a need to enforce control measures to reduce threats to this type of facility.

## KEYWORDS

Microbial surveillance; microbial transmission; persistent vegetative state; *Serratia marcescens; Streptococcus pneumoniae*

## INTRODUCTION

Episodes of infectious disease are important issues in nursing homes, where respiratory infections are most common [1, 2]. Infections can cause high morbidity and mortality among residents [3] since conditions there are ideal for the dissemination of infectious agents. Such conditions are susceptible residents, common exposure sources, people flow, and long-term residence [4]. Development of nosocomial or healthcare-associated infections are associated with two key pathophysiological factors, colonization of pathogenic organisms and impaired host immune defense [5].

Nursing homes that serve patients in a persistent vegetative state (PVS) possess additional distinctions that predispose residents to infections. PVS patients require comprehensive daily care and hygienic practice that is fulfilled solely by nursing home staff. Most PVS patients use intruding devices, well-known risk factors associated with infectious reservoirs [5]. Surveillance studies showed that prevalence of pneumonia in nursing homes for PVS patients was 14.2% [6] and that pathogenic colonization and being susceptible to aspiration pneumonia and systemic infections were associated with tube-fed institutionalized elderly patients [7-9].

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A probable outbreak of respiratory disease involving hospitalization of eight PVS patients in a nursing home alerted the health authority to prompt this study. The purpose was to survey microbe prevalence in respiratory tracts of all PVS patients to determine any person-to-person transmission of microbes. We also surveyed surrounding environments to find reservoirs for suitable control measures.

## METHODS

### Background and setting

Through the national surveillance system for healthcare institutions, a cluster of respiratory infection was reported to the Taiwan Centers for Disease Control in February 2009. It took place in a 45-bed nursing home in northern Taiwan serving PVS patients from low- and middle-income families by a social welfare foundation. When the outbreak occurred, a total of 25 PVS patients resided in three separate wards and received physical therapy of steam inhalation and sputum suction daily.

### Microbial surveillance

Sputum was collected from 24 PVS patients. Environmental samples were taken by using swabs from all possible reservoirs, including tubes, bed railings, spraying humidifiers, faucets, shower heads, mops, water buckets, outlets of reverse osmosis (RO) water, sinks, aprons, CD carts, and telephones. Sputum samples, pretreated with sterile glass beads by vortexing, and environmental swabs were inoculated on blood, chocolate, and MacConkey agar plates. Suspected colonies were selected for identification. Bacteria species and antimicrobial susceptibility were determined by biochemical reaction agar-tubes and the Phoenix Automated Microbiology System (BD, Sparks, MD, U.S.A.) using PMIC/ID-14 and NMIC/ID-4 panels. Serotype of *Streptococcus pneumoniae* was determined by capsule swelling test with pneumococcal antisera (SSI, Copenhagen, Denmark). *Pneumocystis carinii* was detected with polymerase chain reaction [10].

### Bacterial genotyping

Genotyping was performed using pulsed-field gel electrophoresis (PFGE) analysis with the CHEF-DRIII apparatus (Bio-Rad, Hercules, CA, U.S.A.). Ramp and running time were five to 50 seconds and 21 hours with *Spe*I digestion, or five to 15 seconds and eight hours followed by 15 to 45 seconds and 12 hours with *Xba*I digestion for *Serratia marcescens*; five to 30 seconds and 24 hours with *Spe*I digestion for *Pseudomonas aeruginosa* and *Citrobacter koseri*; five to 40 seconds and 23 hours with *Sfi*I digestion for *Proteus mirabilis*; and two to 20 seconds and 21 hours with *Sma*I digestion for *S. pneumoniae*. BioNumerics 4.0 software (Applied Maths, Austin, TX, U.S.A.) was used to determine clonal similarity. Greater than 80% similarity in genetic relatedness was defined as strains with the same pulsotype.

### Statistics

Categorical variables were analyzed using $\chi^2$ statistic or Fisher exact test. In all data analysis, a $p$ value of $< 0.05$ was considered significant.

## RESULTS

### History and patient characteristics

The average age of all 25 PVS patients was 43.8 years (range: 15 to 87 years), with an average residence of 4.7 years (Table 1). In late January 2009, a 26-year-old male, the index case, was hospitalized due to fever, tachypnea, and pneumonia patches in lungs. Within ten days, seven more PVS patients were hospitalized due to respiratory symptoms (32.0% attack rate). They, including six males, came from all three wards, with an average age of 51.6 years (range: 23 to 67 years). Seven hospitalized PVS patients recovered within one week, and the index case had a longer hospital stay.

**TABLE 1: Characteristics of all 25 PVS patients in the nursing home.**

| Characteristic | No. of patients (%) ($n$ = 25) |
|---|---|
| Male | 16 (64.0) |
| Female | 9 (36.0) |
| Respiratory disease | 8 (32.0) |
| Fever (≥ 38°C) | 8 (32.0) |
| Cough | 7 (28.0) |
| Tachypnea | 4 (16.0) |
| Tracheostomy | 16 (64.0) |
| Hospitalized in the past year | 8 (32.0) |
| Duration of residence | |
| More than three years | 20 (80.0) |
| More than five years | 9 (36.0) |

None of the 15 healthcare workers developed respiratory symptoms two weeks before and after the outbreak. Neither did visitors who visited the nursing home one week before. When performing caring duties, healthcare workers wore masks and gloves according to the standard operation protocols. All PVS patients and healthcare workers received seasonal influenza vaccine prior to the outbreak.

*S. marcescens* was isolated from the index case's sputum three days after disease onset in the hospital. Nonetheless, no viral or bacterial cause was concluded. Both clinical characteristics and remedy of antibiotic treatment were not specific for *S. marcescens* infection. However, the outbreak was terminated in a short period due to implementation of control measures, including enhanced hand hygiene, strengthened environment cleanliness and equipment disinfection, and suspending visiting for two weeks.

### Microbial surveillance

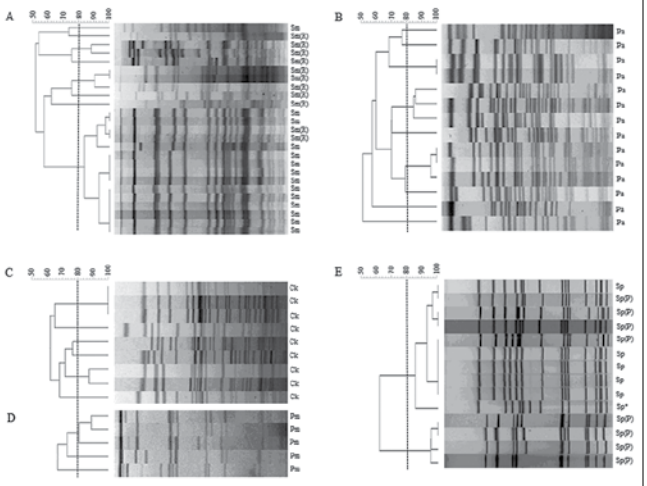
Immediately following the episode, a microbial surveillance of the respiratory tract was conducted for 24 PVS patients, excluding the index case patient, who was then still hospitalized (Table 2). As for Gram-negative bacteria (GNB), 15 PVS patients (62.5%) were colonized with *P. aeruginosa*; 14 patients (58.3%) were colonized with *S. marcescens*, including five of the seven hospitalized and recovered patients (71.4%); and nine and

**TABLE 2: Microbial surveillance from respiratory tracts of 24 PVS patients in the nursing home.**

| Microbe(s) | No. of patients (%) ($n$ = 24)† |
|---|---|
| Gram-negative bacteria | |
| *Pseudomonas aeruginosa* | 15 (62.5) |
| *Serratia marcescens* | 14 (58.3) |
| *Citrobacter koseri* | 9 (37.5) |
| *Proteus mirabilis* | 5 (20.8) |
| *Stenotrophomonas maltophilia* | 3 (12.5) |
| *Klebsiella pneumoniae* | 1 (4.2) |
| Gram-positive bacteria | |
| *Streptococcus pneumoniae* | 6 (25) |
| *Staphylococcus aureus* | 2 (8.3) |
| *Corynebacterium spp.* | 16 (66.7) |
| *Streptococcus spp.* | 12 (50) |
| Fungus | |
| *Pneumocystis carinii* | 4 (16.7) |
| Any one of the above | 0 (0) |
| Any two of the above | 3 (12.5) |
| Any three of the above | 9 (37.5) |
| Any four of the above | 7 (29.2) |
| ≥ five of the above | 5 (20.8) |

†One PVS patient was not included in the surveillance due to his hospitalization. However, *S. marcescens* was isolated from his sputum in the hospital.

**FIGURE 1: PFGE profiles for microbes.**



**Legend**
A: *Serratia marcescens*
B: *Pseudomonas aeruginosa*
C: *Citrobacter koseri*
D: *Proteus mirabilis*
E: *Streptococcus pneumoniae*

Sm, Pa, Ck, Pm, Sp and Sp* strains obtained from PVS patients in this study.
Sm(R), *S. marcescens* strains from the study in respiratory care wards in 2009-2010.
Sp(P), *S. pneumoniae* serotype 23F strains from the National PulseNet Database collections in 2002-2003 and 2007-2009.
Sp, *S. pneumoniae* serotype 23F.
Sp*, *S. pneumoniae* serotype 19F.

five patients were colonized with *C. koseri* and *P. mirabilis*, respectively. As for Gram-positive bacteria, six patients were colonized with *S. pneumoniae* (25%). Polymicrobial colonization was common. 50% of PVS patients were colonized with at least four different microbes.

None of the variables analyzed – including age group, hospitalization in the past year, with tracheostomy, albumin level, length of residence, and *P. aeruginosa* colonization – was significantly associated with *S. marcescens* colonization.

Environmental reservoirs were not found for prevalent microbes. Only *Bacillus cereus*, *Enterobacter cloacae*, and *Stenotrophomonas maltophilia* were identified from the outlets of RO water, mops, and sinks in the nursing station. One of the 15 *P. aeruginosa* strains was resistant to imipenem (6.7%) and none of the *S. marcescens* strains was an extended-spectrum beta-lactamases producer. Both *S. aureus* strains were methicillin-resistant.

### Bacterial genotyping

To clarify possible transmission in the nursing home, all 49 strains of the five major microbes were analyzed by PFGE genotyping (Figure 1). For *S. marcescens*, one major pulsotype was identified for 13 of the 14 strains (92.9%), including all five strains from the seven hospitalized and recovered patients (Figure 1A, *Spe*I digestion). Restriction digestion with *Xba*I gave the same result (data not shown). For *P. aeruginosa*, nine pulsotypes were identified for 14 of the 15 strains (Figure 1B). One *P. aeruginosa* strain could not be digested by *Spe*I. For *C. koseri* and *P. mirabilis*, six and three pulsotypes were identified, respectively (Figures 1C and 1D). For *S. pneumoniae*, one pulsotype was identified for all six strains (100%).

PFGE genotyping was applied to 11 *S. marcescens* strains collected from a microbial surveillance of patients in general respiratory care wards (RCWs) as well (see "Discussion"). Seven pulsotypes were identified, including the major pulsotype in this study, which was observed for two strains from the same hospital in southern Taiwan (Figure 1A). Meanwhile, PFGE genotypes of *S. pneumoniae* strains in this study were submitted to the National PulseNet Database of *S. pneumoniae* in Taiwan. The database included PFGE genotypes of *S. pneumoniae* strains isolated from patients with invasive infections throughout Taiwan during 2002-2003 and 2007-2009 (unpublished data). In the database, a total of 199 *S. pneumoniae* serotype 23F strains were classified into nine pulsotypes, including two major pulsotypes consisting of 90 (45.2%) and 87 (43.7%) strains, respectively. All six *S. pneumoniae* strains in this study shared the same pulsotype as the 90 strains from the database (Figure 1E).

## DISCUSSION

In this study, we found that polymicrobial colonization was common, GNB colonization was prevalent, and person-to-person transmission of *S. marcescens* and *S. pneumoniae* was evident among PVS patients.



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A microbial surveillance for patients residing in RCWs conducted in 2009-2010 revealed that 45.9% and 14.9% of patients were colonized with *P. aeruginosa* and *S. marcescens* in their respiratory tracts, respectively (our unpublished data). The *S. marcescens* colonization rate was significantly lower than that in PVS patients ($p < 0.001$), while the *P. aeruginosa* colonization rate was not ($p = 0.16$).

*P. aeruginosa* constituted a high proportion of pathogenic GNB from respiratory tracts of tube-fed elderly patients (31% and 34% in two studies) [7, 11]. *P. aeruginosa* (23.4%) and *S. marcescens* (10.8%) were major microbes in a bacterial surveillance for respiratory aspirates from patients in RCWs [12]. *P. aeruginosa* was well-known for its colonizing tendency for respiratory equipment and thriving in oropharynx. *S. marcescens* emerged as an opportunistic pathogen to cause outbreaks, likely attributable to its rapid spreading and innumerable heterogeneous clones, its potential reservoirs in infected or colonized carriers and inanimate objects, and its correlation with use of intruding tubes [13-19]. A previous study reported that 89% of PVS patients in Taiwan used a nasogastric tube (NGT) for feeding [6]. Most PVS patients in our study also used an NGT for feeding.

In our study, one pulsotype each was dominant for *S. marcescens* and *S. pneumoniae*. In contrast, diverse pulsotypes were identified for *P. aeruginosa*, *C. koseri*, and *P. mirabilis* in our study as well as for *S. marcescens* from RCW patients and for *S. pneumoniae* from the National PulseNet Database. These results clearly suggest that *S. marcescens* and *S. pneumoniae* were transmitted among PVS patients in the nursing home. Furthermore, the dominant pulsotype for either *S. marcescens* or *S. pneumoniae* in the nursing home was not unique, since it was also found in *S. marcescens* strains from RCW patients and in *S. pneumoniae* strains from the National PulseNet Database. This result indicates that both dominant pulsotypes for the *S. marcescens* and *S. pneumoniae* strains were circulating in the community as well. Since at least 37.5% of all nosocomial infections were due to cross-transmission [20], microorganisms from outside environments constituted a great public health concern.

There were limitations to our study. First, it was carried out in one single nursing home with a small patient number. However, the entire PVS population was included, except the index case patient, and the findings represented the real situation in this facility. Second, no risk factor was found in association with *S. marcescens* colonization, suggesting that further studies are required. Third, the exact mode of microbial cross-transmission was not identified. The outbreak occurred during a one-week holiday; infectious reservoirs were likely eliminated during environmental disinfection. Nonetheless, clonal transmission among PVS patients was supported by bacterial genotyping results.

In conclusion, we report the cross-transmission of *S. marcescens* and *S. pneumoniae* in a nursing home serving PVS patients, highlighting the threat to this type of healthcare facility and the importance of comprehensive control measures.

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# Can the use of assistive technology and interactive therapeutic robots in nursing homes contribute to the spread of infectious disease?

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**ABSTRACT**

**Background:** There is an increasing use of assistive technology and interactive therapeutic robots in nursing homes. However, little is known about the possible risks for transmitting infectious diseases through the use of such devices.

**Methods:** Representative surface samples of two multipurpose hygiene chairs and two interactive therapeutic robots were collected on a weekly basis at two nursing homes over a period of two months.

**Results:** We found that both robots and hygiene chairs may contribute to pathogen transmission.

**KEY WORDS**
Assistive technology, interactive therapeutic robots, HAI, multipurpose hygiene chairs, nursing home

## BACKGROUND

Norwegian municipalities are increasingly using assistive technology and interactive therapeutic robots in their nursing homes [1]. Some of these products come in close physical and protracted contact with several patients and might constitute a source of infection. Little is known about the possible risks for transmitting infectious diseases through these devices. In this study we focused on multipurpose hygiene chairs and PARO interactive therapeutic robots.

Multipurpose hygiene chairs are used for washing and cleaning routines that require assistance from nursing staff (Figure 1).

PARO robots (Figure 2) are used in dementia care [2] to stimulate patients and cleaning done by the nursing home staff can only be done in a superficial way. Washing the interactive robot is not possible so that the artificial fur needs to be replaced by the distributor.

We collected representative surface samples of two hygiene chairs and two robots on a weekly basis over a period of two months at two nursing homes and analyzed the samples for the presence of clinically relevant microorganisms.

## MATERIAL & METHODS

### *Nursing homes*

Two nursing homes of approximately the same size, but located in different municipalities and with slightly different management structures took part in the study. Both nursing homes have implemented infection control programs.

### *Multipurpose hygiene chairs and PARO robots*

Four hygiene chairs (Carendo, ArjoHuntleigh, Sweden), two in each nursing home, were labeled according to the following scheme NxCx (N for nursing home 1 or 2, C for chair 1 or 2). N1C1 was not in use, due to necessary maintenance, but served as reference. N2C2 had been used by one resident only. N1C2 and N2C1 were in use by more than one resident, and no special precautions other than visible cleaning have been done. All hygiene chairs were visible clean according to applied standards [3] before sampling.

Four PARO robots, two in each nursing home, labeled NxPx (N for nursing home 1 or 2, P for robot 1 or 2). N1P1 and N1P2 were in sporadic use during the sampling period. For all PARO robots, there was no cleaning performed between the use by different residents.

**Conflicts of interest:** None to report.
**Acknowledgement**: We would like to thank Larvik and Nøtterøy municipalities, HSN Innovatoriet and the regional research fund "Oslofjordfondet" for financing this project.

**FIGURE 1: Multipurpose hygiene chair Carendo, ArjoHuntleigh [from: http://www.arjohuntleigh.com/products/hygiene-systems/showering/shower-chairs/carendo/ ]**

**FIGURE 2: PARO interactive therapeutic robot in close contact with resident**

***Swab sampling***

Sterile flocked swabs were moistened in sterile water prior to surface swabbing of approximately 100 $cm^2$. Two duplicate samples were taken each time and stored in either sterile water for bacterial cultivation or RNAlater for PCR analysis respectively.

Duplicate surface samples were taken with the M40 Transport system for bacterial cultivation.

***ATP analysis***

Duplicate ATP surface samples were taken according to the manufacturer's protocol (Hygiena, UltraSnap™ surface test).

***Contact sampling with dry nutrient medium plates***

Duplicate surface contact samples were taken with Rida®Count test plates for total bacteria and *Staphylococcus aureus* counts.

***MRSA***

*Staphylococcus aureus* colonies from Rida®Count *Staph. aureus* test plates were transferred to MRSASelect™ agar (BioRad).

***Bacteriology from swab samples***

Duplicates swab samples were pooled and transferred to the following selective media:

- **E. coli/coliform and ESBL detection**: Brilliance E.coli/coliform selective Agar and ESBL agar (Oxoid).
- **Enterococci and VRE:** HiCrome™ Rapid Enterrococi agar, VancoScreening Brain Heart Infusion agar (NordicAST).
- **MRSA**: Samples were grown for 48 hours in PHMB enrichment broth without cefoxitin, [4] and screened for MRSA. Results have been validated by PCR [5].
- **Clostridium difficile**: Samples were grown anaerobically in CCFT-broth [6] and plated on Braziers *Clostridium difficile* selective agar, after two and ten days. Results have been validated by PCR [7].

Antibiotic resistant strains were identified by MALDI-TOF MS Biotyper (Bruker Daltonik, Germany).

***PCR***

qPCR was performed for influenza A and norovirus 1 and 2 were done as described in [8].

## RESULTS

PARO robots N1P1 and N1P2 were not in daily use, which could explain the lower arithmetic mean relative light units (RLU) values, i.e., luciferase activity, compared to the frequently used N2P1 and N2P2 (Figure 3, a). By contrast, N1P1 and N1P2 gave higher arithmetic mean CFU for both aerobic (Fig. 3, b) and *Staphylococcus aureus* counts (Fig. 3, c).

One sampling of N2P2 gave a single atypical colony on the MRSASelect™ agar. This colony was subsequently identified as methicillin resistant *Staphylococcus epidermis* by MALDI-TOF.

The hygiene chair N1C1 was not in use at the time of testing which may explain the results of the ATP monitoring. However the aerobic count had an arithmetic mean CFU/ml up



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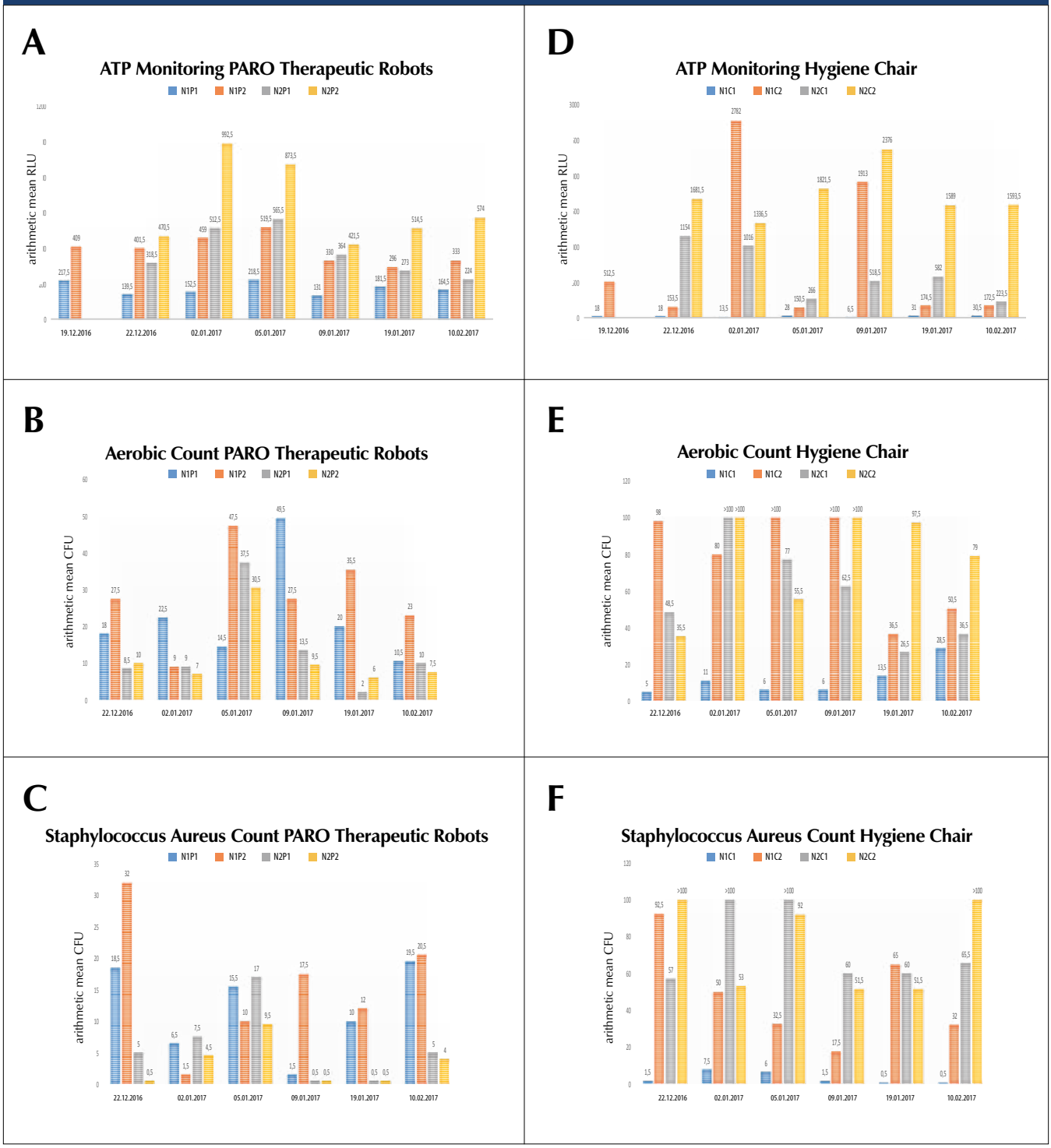
**FIGURE 3: Serial measurements (mean values) of ATP (a,d), aerobic counts (b,e) and *Staphylococcus aureus* counts (c,f) for PARO robots (a,b,c) and hygiene chairs (d,e,f).**




to 28.5 (Fig. 3). All other Hygiene chairs were sampled after standard cleaning. These showed both a high aerobic count (Fig. 3, e), as well as a higher degree of contamination with *Staphylococcus aureus* (Fig. 3, f). Furthermore, the ATP monitoring (Fig. 3, d) revealed that biological contamination in nursing home two was higher overall than in nursing home one. One Rida®Count sampling of N2C1 gave typical colonies for MRSA on the MRSASelect™ agar. The latter was, however, not validated by other methods. Coliform bacteria (Table 1) were found on all four robots. N1P1 tested positive for *Enterobacteriaceae* at one sampling (Table 1, N1P1).

**TABLE 1: Result of selective bacterial cultivation. (-) no growth, (*) no growth of Enetrobacteriaceae, but cefotoxitin resistant Pseudomonas fulva and Pseudomonas putida, (**) Enterococcus casseliflavus**

**N1P1**

| Dato | *E.coli* | Colif. | ESBL | Entero | VRE |
|---|---|---|---|---|---|
| 19.12.16 | - | - | - | - | - |
| 22.12.16 | - | - | - | + | - |
| 02.01.17 | - | - | - | - | - |
| 05.01.17 | - | - | - | - | - |
| 09.01.17 | - | - | - | - | - |
| 19.01.17 | - | - | - | - | - |
| 10.02.17 | - | +++ | - | | - |

**N1P2**

| Dato | *E.coli* | Colif. | ESBL | Entero | VRE |
|---|---|---|---|---|---|
| 19.12.16 | - | - | - | - | - |
| 22.12.16 | - | +++ | - | - | - |
| 02.01.17 | - | +++ | - | - | - |
| 05.01.17 | - | ++ | - | - | - |
| 09.01.17 | - | + | - | - | - |
| 19.01.17 | - | - | - | - | - |
| 10.02.17 | - | - | - | - | - |

**N2P1**

| Dato | *E.coli* | Colif. | ESBL | Entero | VRE |
|---|---|---|---|---|---|
| 22.12.16 | - | - | - | - | - |
| 02.01.17 | - | ++ | - | - | - |
| 05.01.17 | - | ++ | - | - | - |
| 09.01.17 | - | - | | - | - |
| 19.01.17 | - | + | - | - | - |
| 10.02.17 | - | - | - | - | - |

**N2P2**

| Dato | *E.coli* | Colif. | ESBL | Entero | VRE |
|---|---|---|---|---|---|
| 22.12.16 | - | - | - | - | - |
| 02.01.17 | - | +++ | - | - | - |
| 05.01.17 | - | ++ | - | - | - |
| 09.01.17 | - | - | - | - | - |
| 19.01.17 | - | - | - | - | - |
| 10.02.17 | | ++ | - | - | - |

**N1C1**

| Dato | *E.coli* | Colif. | ESBL | Entero | VRE |
|---|---|---|---|---|---|
| 19.12.16 | - | - | - | - | - |
| 22.12.16 | - | - | - | - | - |
| 02.01.17 | - | - | - | - | - |
| 05.01.17 | - | - | - | - | - |
| 09.01.17 | - | - | - | + | - |
| 19.01.17 | - | - | - | - | - |
| 10.02.17 | - | - | - | - | - |

**N1C2**

| Dato | *E.coli* | Colif. | ESBL | Entero | VRE |
|---|---|---|---|---|---|
| 19.12.16 | - | +++ | -* | +++ | - |
| 22.12.16 | - | ++ | -* | +++ | - |
| 02.01.17 | ++ | ++ | -* | +++ | - |
| 05.01.17 | - | - | - | - | - |
| 09.01.17 | - | +++ | -* | +++ | - |
| 19.01.17 | - | - | - | - | - |
| 10.02.17 | - | - | - | - | - |

**N2C1**

| Dato | *E.coli* | Colif. | ESBL | Entero | VRE |
|---|---|---|---|---|---|
| 22.12.16 | (+) | - | -* | - | - |
| 02.01.17 | - | - | | - | - |
| 05.01.17 | - | (+) | -* | + | +** |
| 09.01.17 | - | - | - | + | +** |
| 19.01.17 | - | - | - | - | - |
| 10.02.17 | - | - | - | - | - |

**N2C2**

| Dato | *E.coli* | Colif. | ESBL | Entero | VRE |
|---|---|---|---|---|---|
| 11.12.16 | - | - | - | ++ | - |
| 02.01.17 | - | - | - | - | - |
| 05.01.17 | - | - | - | - | - |
| 08.01.17 | - | - | - | - | - |
| 09.01.17 | - | - | - | - | - |
| 19.02.17 | - | - | - | + | - |
| 10.02.17 | - | - | - | ++ | - |



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Except for N1C2, all hygiene chairs showed little or no *E. coli* or other coliform bacteria (Table 1). N2C2 tested positive for *Enterobacteriaceae*. Cefoxitin resistant *Pseudomanas fulva* and *Pseudomanas putida* were found on samples obtained from N2C1 and N1C2. N2C1 tested positive for a vancomycin-resistant enterococci (VRE), namely *Enterococcus casseliflavus* (Table 1).

None of the samples tested positive for viral nucleic acid or *Clostridium difficile*.

## DISCUSSION

This study has several limitations, such as the sample size, duration and number of participating nursing homes. However, the authors believe that this study gives an indication of the possible role that assistive technology and interactive therapeutic robots have in the transmission of microorganisms and that further research in this field is required to increase patient safety in nursing homes.

PARO robots are often used by several residents and shared between different nursing home sections. It is difficult to clean the artificial fur; it can only be removed and washed by the distributor. However, based on ATP monitoring and aerobic count (Fig. 3, a and b) it seems that bacteria do not long remain viable on the PARO. Nevertheless, it seems also that the PARO robot may be a beneficial environment for *Staphylococcus aureus* (Fig. 3, c). Further studies are needed to confirm this.

The finding that biological contamination in nursing home two was higher overall than in nursing home one, may be due to different managerial structures of the cleaning services. Cleaning in nursing home one is done by municipal employees only working in this particular nursing home, whereas cleaning personnel in nursing home two is done by employees working in different municipal institutions.

The presence of coliform bacteria (Table 1) on the fur of the PARO robot may be due to inadequate hand hygiene [9], and could indicate that the robot is contributing in the transfer of microorganisms between different patient zones.

The hygiene chairs showed a high level of bacterial contamination, even after standard cleaning. Interestingly, N1C1 which was not in use showed an increase in the aerobic count. This may indicate that the rough surface structure of the hygiene chairs may accumulate airborne bacteria. In general, this study has shown that current cleaning procedures for hygiene chairs are not adequate. One of the chairs in this study, N1C2, used by several residents, tested positive for cefotoxitin-resistant *P. fulva* and *P. putida*.

That influenza virus, norovirus and *Clostridium difficile* were not found may be due to unrelated factors. The national peak of influenza virus infections in Norway was in week 51 [10], three weeks before the first samples were taken. Furthermore, there were no ongoing infections in the nursing homes related to these agents and there have been only 46 clinical CDI cases in 2016 in the municipalities where the two nursing homes are located.

This study demonstrate the need for further research on the role of assistive technology and interactive therapeutic robots in pathogen distribution and the need for new cleaning procedures, a constant evaluation of infection control systems, as well as improved product design.

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# Estimating the extent of asymptomatic COVID-19 and its potential for community transmission: Systematic review and meta-analysis

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## ABSTRACT

***Background:*** Knowing the prevalence of true asymptomatic coronavirus disease 2019 (COVID-19) cases is critical for designing mitigation measures against the pandemic. We aimed to synthesize all available research on asymptomatic cases and transmission rates.

***Methods:*** We searched PubMed, Embase, Cochrane COVID-19 trials, and Europe PMC for primary studies on asymptomatic prevalence in which
(1) the sample frame includes at-risk populations, and;
(2) follow-up was sufficient to identify pre-symptomatic cases. Meta-analysis used fixed-effects and random-effects models. We assessed risk of bias by combination of questions adapted from risk of bias tools for prevalence and diagnostic accuracy studies.

***Results:*** We screened 2,454 articles and included 13 low risk-of-bias studies from seven countries that tested 21,708 at-risk people, of which 663 were positive and 111 asymptomatic. Diagnosis in all studies was confirmed using a real-time reverse transcriptase–polymerase chain reaction test. The asymptomatic proportion ranged from 4% to 41%. Meta-analysis (fixed effects) found that the proportion of asymptomatic cases was 17% (95% CI 14% to 20%) overall and higher in aged care (20%; 95% CI 14% to 27%) than in non-aged care (16%; 95% CI 13% to 20%). The relative risk (RR) of asymptomatic transmission was 42% lower than that for symptomatic transmission (combined RR 0.58; 95% CI 0.34 to 0.99, p = 0.047).

***Conclusions:*** Our one-in-six estimate of the prevalence of asymptomatic COVID-19 cases and asymptomatic transmission rates is lower than those of many highly publicized studies but still sufficient to warrant policy attention. Further robust epidemiological evidence is urgently needed, including in subpopulations such as children, to better understand how asymptomatic cases contribute to the pandemic.

## KEYWORDS

Emerging or re-emerging diseases, epidemiology, evidence-based medicine, public health policy

## RÉSUMÉ

***Historique :*** Il est essentiel de connaître la prévalence des véritables cas asymptomatiques de maladie à coronavirus 2019 (COVID-19) pour concevoir des mesures d'atténuation de la pandémie. Les chercheurs ont voulu synthétiser toutes les recherches disponibles sur les cas asymptomatiques et les taux de transmission.

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**Contributors:** Conceptualization, OB, MC, KB, PG; Methodology, OB, MC, KB, JC, M-LM, PG; Software, JC; Formal Analysis, OB, MC, KB, PG; Data Curation, MC, KB, M-LM, PG; Writing – Original Draft, OB, MC, KB, JC, M-LM, PG; Writing – Review & Editing, OB, MC, KB, JC, M-LM, PG; Visualization, OB; Supervision, PG; Project Administration, OB.

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***Méthodologie :*** Les chercheurs ont fouillé les bases de données PubMed, Embase, Cochrane pour trouver les études sur la COVID-19, et Europe PMC pour colliger les études primaires sur la prévalence des cas asymptomatiques dans lesquelles 1) le cadre d'échantillonnage incluait une population à risque et 2) le suivi était suffisant pour dépister les cas présymptomatiques. La méta-analyse a fait appel à des modèles d'effets fixes et d'effets aléatoires. Nous avons évalué le risque de biais par une combinaison de questions adaptées d'outils sur les risques de biais des études de prévalence et de précision diagnostique.

***Résultats :*** Les chercheurs ont extrait 2 454 articles, dont 13 études à faible risque de biais de sept pays dans lesquelles 21 708 personnes à risque ont subi le test de dépistage, soit 663 cas positifs et 111 cas asymptomatiques. Dans toutes les études, le diagnostic a été confirmé au moyen du test d'amplification en chaîne par polymérase après transcriptase inverse en temps réel. La proportion de cas asymptomatiques se situait entre 4 % et 41 %. La méta-analyse (à effets fixes) a établi que la proportion de cas asymptomatiques s'élevait à 17 % (IC à 95 %, 14 % à 20 %) dans l'ensemble, mais qu'elles étaient plus élevées dans les soins aux aînés (20 %; IC à 95 %, 14 % à 27 %) qu'auprès du reste de la population (16 %; IC à 95 %, 13 % à 20 %). Le risque relatif [RR] de transmission de cas asymptomatiques était plus faible de 42 % que celui de cas symptomatiques (RR combiné de 0,58; IC à 95 %, 0,34 à 0.99, p = 0,047).

***Conclusions :*** L'évaluation de la prévalence d'un sixième de cas asymptomatiques de COVID-19 et de taux de transmission de cas asymptomatiques est inférieure à celle de nombreuses études hautement publicisées, mais suffit tout de même pour justifier l'intérêt de la santé publique. D'autres données épidémiologiques solides s'imposent de toute urgence, y compris dans des sous-populations comme les enfants, pour mieux comprendre l'effet des cas asymptomatiques sur la pandémie.

**MOTS-CLÉS**
Epidémiologie, maladie émergente ou réémergente, médecine fondée sur des données probantes, politique de santé publique

## INTRODUCTION

Asymptomatic cases of any infection are of considerable concern for public health policies to manage epidemics. Such asymptomatic cases complicate the tracking of an epidemic and prevent reliable estimates of transmission, tracing, and tracking strategies for containing an epidemic through isolation and quarantine. This has been a significant concern in the current coronavirus disease 2019 (COVID-19) pandemic [1].

The possibility of asymptomatic transmission of COVID-19 cases was first raised by a case report in China in which a traveller from Wuhan was presumed to have transmitted the infection to five other family members in other locations while she remained asymptomatic for the entire 21-day follow-up period [2]. Subsequently, other reports confirmed not only the possibility of such transmission but began quantifying the potential proportions. For example, the outbreak on the Diamond Princess cruise ship included a substantial proportion of asymptomatic cases after widespread testing of those on board the ship [3]. An early rapid review by the Centre for Evidence-Based Medicine in Oxford, United Kingdom, found that the estimated proportion of asymptomatic COVID-19 cases ranged from 5% to 80% [4]. However, many of the identified studies were either poorly executed or poorly documented, making the validity of these estimates questionable.

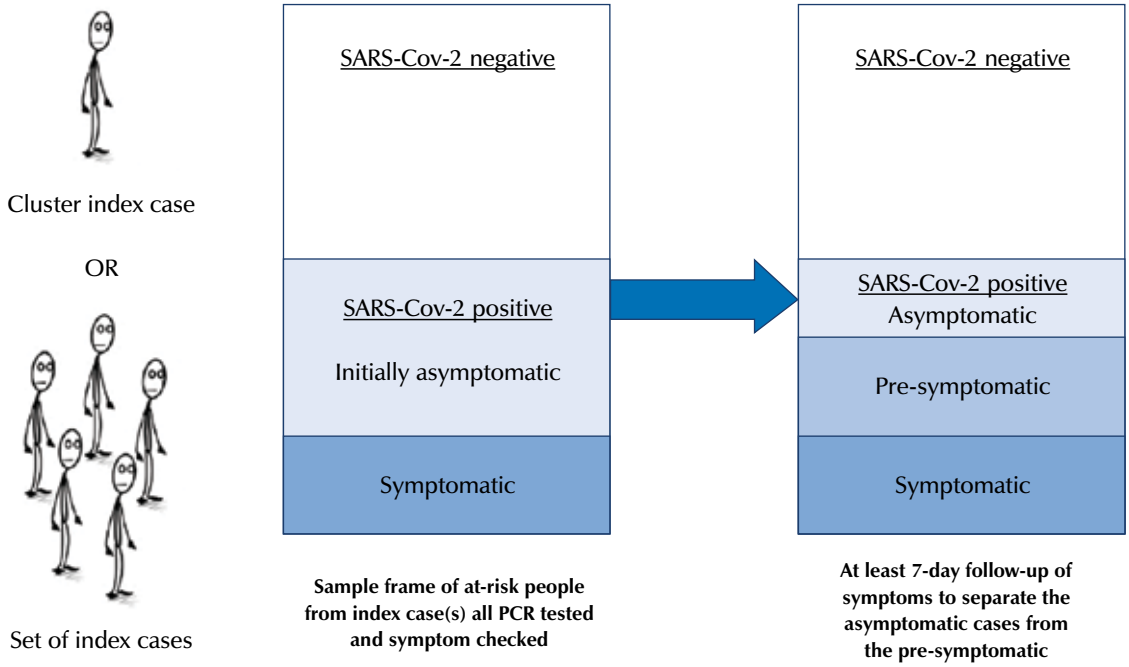
We therefore sought to identify all studies that had attempted to estimate the proportion of asymptomatic COVID-19 cases, select those with low risk of bias, and synthesize them to provide an overall estimate and potential range. We also aimed to estimate the rate of forward transmission from asymptomatic cases if sufficient data were found.

## METHODS

We conducted a systematic review and meta-analysis using enhanced processes with an initial report completed within two weeks and daily short team meetings to review progress, plan the next actions, and resolve discrepancies and other obstacles [5]. We also used locally developed open access automation tools and programs such as the Polyglot Search Translator, SearchRefiner, and the SRA Helper to design, refine, and convert our search strategy for all the databases we searched and to speed up the screening process [6]. We searched the PROSPERO database to rule out the existence of a similar review and PubMed, Embase, and Cochrane COVID-19 trials for published studies and Europe PMC for pre-prints from January 2020 to July 20, 2020. A search string composed of MeSH terms and words was developed in PubMed and was translated to be run in other databases using the Polyglot Search Translator. The search strategies for all databases are presented in Supplemental Appendix 1. We also conducted forward and backward citation searches of the included studies in the Scopus citation database.

We restricted publication types to reports of primary data collection released in full (including pre-prints) with sufficient details to enable a risk-of-bias assessment, and we contacted authors for clarifications on follow-up times and sampling frames. We anticipated that cross-sectional prevalence surveys with follow-up and cohort studies would be the bulk of eligible reports. No restrictions on language were imposed. We excluded studies for the following reasons: sampling frame in part determined by presence or absence of symptoms; no or unclear follow-up; no data on asymptomatic cases; single case study or small cluster; modelling or simulation studies (but sources of real data were checked for possible inclusion); non–severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) studies; antiviral treatment studies; and study protocols, guidelines, editorials, or historical accounts without data to calculate primary outcomes.

**FIGURE 1: Depiction of ideal study flow and criteria used for study inclusion:**
**(1) sample frame of at-risk people, and;**
**(2) adequate follow-up on symptoms**
SARS-Cov-2 = Severe acute respiratory syndrome coronavirus 2; PCR = Polymerase chain reaction




**Participants**
We included studies of people of any age in which all those at risk of contracting SARS-CoV-2 were tested regardless of presence or absence of symptoms; diagnosis was confirmed by a positive result on a real-time reverse transcriptase–polymerase chain reaction (RT-PCR), and all cases had a follow-up period of at least seven days to distinguish asymptomatic cases from pre-symptomatic cases **(Figure 1).**

**Outcomes**
Our primary outcome was the proportion of all people with SARS-Cov-2 infection who were completely asymptomatic at the time of the test and throughout the follow-up period, where the denominator included all tested individuals in the study sample whose result was positive, and the numerator included those who tested positive and had no symptoms. Our secondary outcome was estimate of onward transmission of the infection from asymptomatic cases.

**Study selection and screening**
Two authors (OB and MC) independently screened titles, abstracts, and full texts according to eligibility criteria. All discrepancies were resolved via group discussion with the other authors. Reasons for exclusion were documented for all full-text articles deemed ineligible (Supplemental Appendix 2); see the Preferred Reporting Information for Systematic Reviews and Meta-Analyses diagram **(Figure 2).**

**Data extraction**
Three authors (OB, MC, KB) used a Microsoft Excel spreadsheet to extract the following information:

1. Methods: study authors, year of publication, country, publication type, duration of study, duration of follow-up
2. Participants: sample size, age (mean or median, range), setting (community, province, aged care facility, hospital, screening clinic), presence or absence of symptoms, test results
3. History of illness and diagnosis: type of test; numerator (number of asymptomatic); denominator (sampling frame); mildly symptomatic or symptomatic subjects; and number or proportion of people infected by the asymptomatic case.
4. Case definitions were as follows:
   - **Asymptomatic:** confirmed via any testing specified earlier with report of no symptoms for the duration of sufficient follow-up to differentiate from pre-symptomatic cases.
   - **Exposure:** contact with a confirmed case or potential contact with another pre-symptomatic person (e.g., came from an endemic area or linked with an infected traveller).

The World Health Organization recommends that "for confirmed asymptomatic cases, the period of contact is measured as the two days before through the 14 days after the date on which the sample was taken which led to confirmation" (7, p.11).


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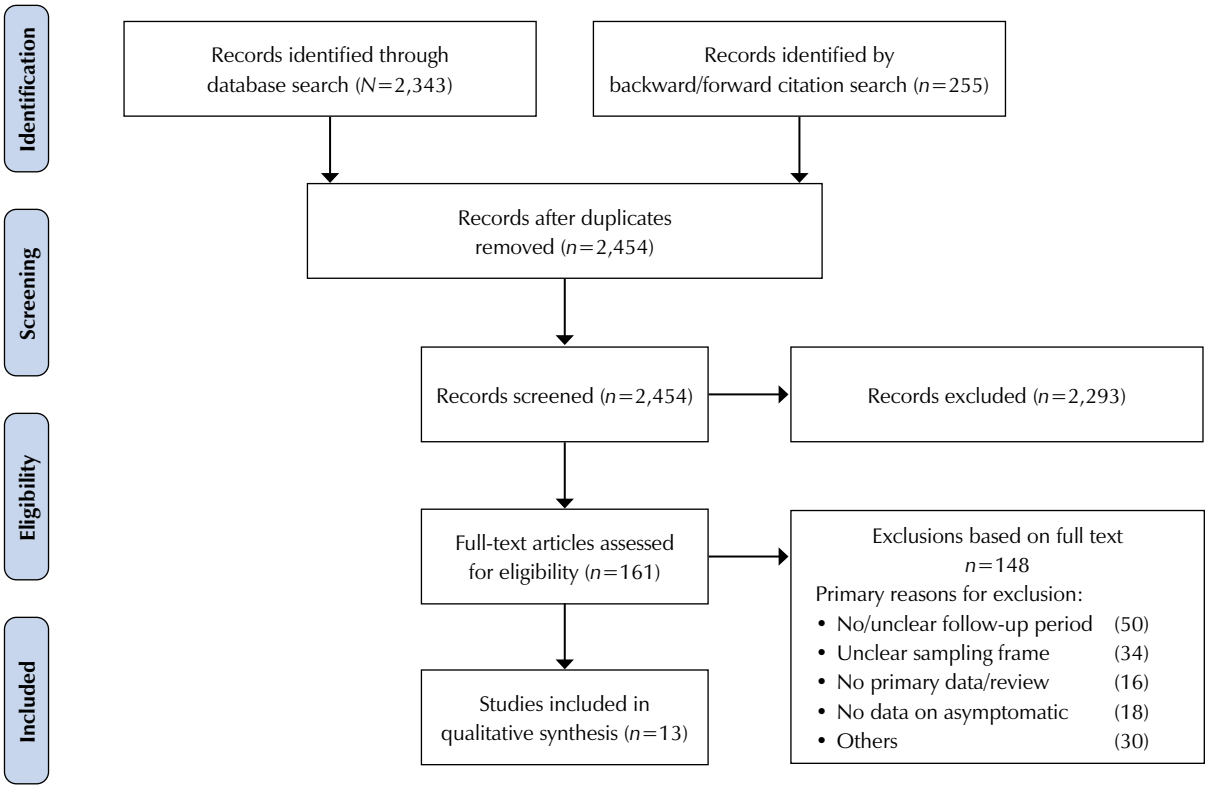
**FIGURE 2: Screening and selection of articles**




### Risk-of-bias assessment

Three authors (OB, MC, KB) assessed the risk of bias of potentially includable studies. We used a combination of risk-of-bias tools for prevalence studies and diagnostic accuracy and adapted the key signaling questions on sampling frame, ascertainment of infectious disease status, acceptability of methods to identify denominators, case definition of *asymptomatic* for the numerator, and length of follow-up, as shown in **Table 2** and in Supplemental Appendix 3 in full [8,9].

### Data analysis

We estimated the proportion of COVID-19 cases who were asymptomatic for each included study population, assuming a binomial distribution and calculating exact Clopper–Pearson confidence intervals. We then pooled data from all included studies using:

(1) fixed-effects meta-analysis and

(2) random-effects meta-analysis. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC); the FREQ procedure was used for individual studies and the fixed-effects meta-analysis; the NLMIXED procedure was used for the random-effects meta-analysis. We also meta-analyzed the forward transmission rates from asymptomatic and symptomatic cases when there were sufficient data and report the pooled RR comparing the two. We planned to undertake subgroup analysis for age (between studies, and within studies when age was reported separately for asymptomatic and symptomatic cases). Because the analysis included only studies deemed to be of high quality on items 1 and 2 after risk-of-bias appraisal, no sensitivity analysis of high- versus low-quality studies was undertaken. Instead, we did a sensitivity analysis in which we omitted studies with a follow-up duration of less than 14 days.

## RESULTS

A total of 2,454 articles were screened for title and abstract, and 161 full-text articles were assessed for inclusion (Figure 2). Major reasons for exclusion were inadequate sampling frame and insufficient follow-up time to accurately classify the asymptomatic cases. The full list of excluded studies with reasons is presented in Supplemental Appendix 2. Thirteen articles – nine published and four preprints – from seven countries (China, $n = 4$; United States, $n = 4$; Taiwan, $n = 1$; Brunei, $n = 1$; Korea, $n = 1$; France, $n = 1$; and Italy, $n = 1$) that tested 21,708 close contacts of at least 849 confirmed COVID-19 cases, of which 663 were positive and 111 were asymptomatic, met the eligibility criteria for the estimation of the primary outcome [10–22].The sampling frames of the selected studies included residents of skilled nursing facilities (SNFs; 10, 12, 15, 19, 20); high-risk close contacts of confirmed COVID-19 cases [11, 13, 14, 17, 18, 21]; and a whole district surveillance program in Italy [16].

**TABLE 1: Characteristics of included studies (*N* = 13)**

| Study (country) and publication status | Study population (sampling frame) | Sample size and age | Diagnostic testing and frequency | Length of follow-up for asymptomatic cases |
|---|---|---|---|---|
| Roxby *et al* [20] (United States) Published | Residents of independent and assisted living communities (Facility 1) in Seattle after two confirmed cases between 5 and 9 Mar | *N* = 79; mean age of cohort 86 y | Nasal swab, RT-PCR, twice, 1 wk apart | 7 days |
| Patel *et al* [19] (United States) Published | Residents and staff of skilled nursing facility in Illinois on 15 Mar | *N* = 126; median age of cases 82 y. | Nasal swab, RT-PCR, once | 30 days |
| Dora *et al* [15] (United States) Published | Residents of skilled nursing facility in Veterans Affairs Greater Los Angeles Healthcare System between 29 Mar and 23 Apr | *N* = 99; median age of cohort 75 y. | Nasal swab, RT-PCR, repeated every 10 d | At least 14 days |
| Blain *et al* [12] (France) Published | Nursing home residents in France tested weekly since early Mar | *N* = 79; mean age 86 y | Nasal swab, RT-PCR, repeated weekly | 6 weeks |
| Arons *et al* [10] (United States) Published | Residents of skilled nursing facility (Facility A) in Seattle after a confirmed case on 1 Mar | *N* = 86; mean age of cohort 77 y, mean age of cases 79 y. | Nasal swab, RT-PCR, twice, 1 wk apart | 7 days |
| Zhang *et al* [22] (China) Published | Close contacts of confirmed cases between 28 Jan and 15 Mar in Guangzhou, China | *N* = 369; median age 35 y. | Nasal swab, RT-PCR, at least twice | 14 days |
| Tian *et al* [21] (China) Preprint | Close contacts (coworkers, family members, customers) of a confirmed supermarket employee (super-spreader) in Liaocheng, China. | *N* ≃ _8,000; mean age of cases 48 y | Nasal swab, RT-PCR, repeated every 2 days | 16±6.15 days |
| Cheng *et al* [14] (Taiwan) Published | High-risk close contacts (household members, HCWs) of first 100 cases in Taiwan | *N* = 849; mean age of cohort 42 y, mean age of cases 41 y | Nasal swab, RT-PCR, repeated during 14 d quarantine | 14 days |
| Lavezzo *et al* [16] (Italy) Published | Majority of population of Italian town of Vò after a COVID-19 death on 21 Feb. | *N* = 2,812; mean age of cohort 47 y, mean age of cases 58 y | Nasal swab, RT-PCR, twice, 7–14 d apart | 7-14 days |
| Bi *et al* [11] (China) Published | Close contacts of cases confirmed before 9 Feb in Shenzhen, China | *N* = 1,286; mean age of cohort 38 y, mean age of cases 43 y | Nasal swab, RT-PCR, repeated during 14 d quarantine | 95% followed up for ≥12 days |
| Chaw *et al* [13] (Brunei) Preprint | Bruneian attendants of a religious event in Malaysia, where a confirmed case was present | *N* = 1,830; mean age of cohort 31 y, mean age of cases 33 y | Nasal swab, RT-PCR, repeated weekly | 14 days |
| Luo *et al* [17] (China) Preprint | Close contacts of 347 confirmed COVID-19 patients identified between 13 Jan and 6 Mar in Guangzhou, China | *N_ _= 4,950; mean age of cohort 38 y, mean age of cases 44 y* | Nasal swab, RT-PCR, repeated every 2 d | 14 days |
| Park *et al* [18] (Korea) Published | Employees, residents, and visitors of a commercial and residential building where a confirmed case worked | *N_ _= 1,143; mean age of cohort 38 y* | Nasal swab, RT-PCR, repeated during 14 d quarantine | 14 days |

*RT-PCR = Reverse transcriptase–polymerase chain reaction; HCWs = Health care workers; COVID-19 = Coronavirus disease 2019*

**TABLE 2: Comparison of secondary transmission rates**

| Study | Asymptomatic transmission rate No./*N* (%) | Asymptomatic transmission rate No./*N* (%) | Relative risk |
|---|---|---|---|
| Zhang *et al* (22) | 1/119 (0.8) | 11/250 (4.4) | 0.2 |
| Cheng *et al* (14) | 0/91 (0) | 22/2644 (0.8) | 0.66 |
| Chaw *et al* (13) | 15/691 (2.2) | 28/1010 (2.8) | 0.78 |
| Luo *et al* (17) | 1/305 (0.3) | 117/2305 (5.1) | 0.06 |
| Park *et al* (18) | 0/4 (0) | 34/221 (15.4) | 0.72 |



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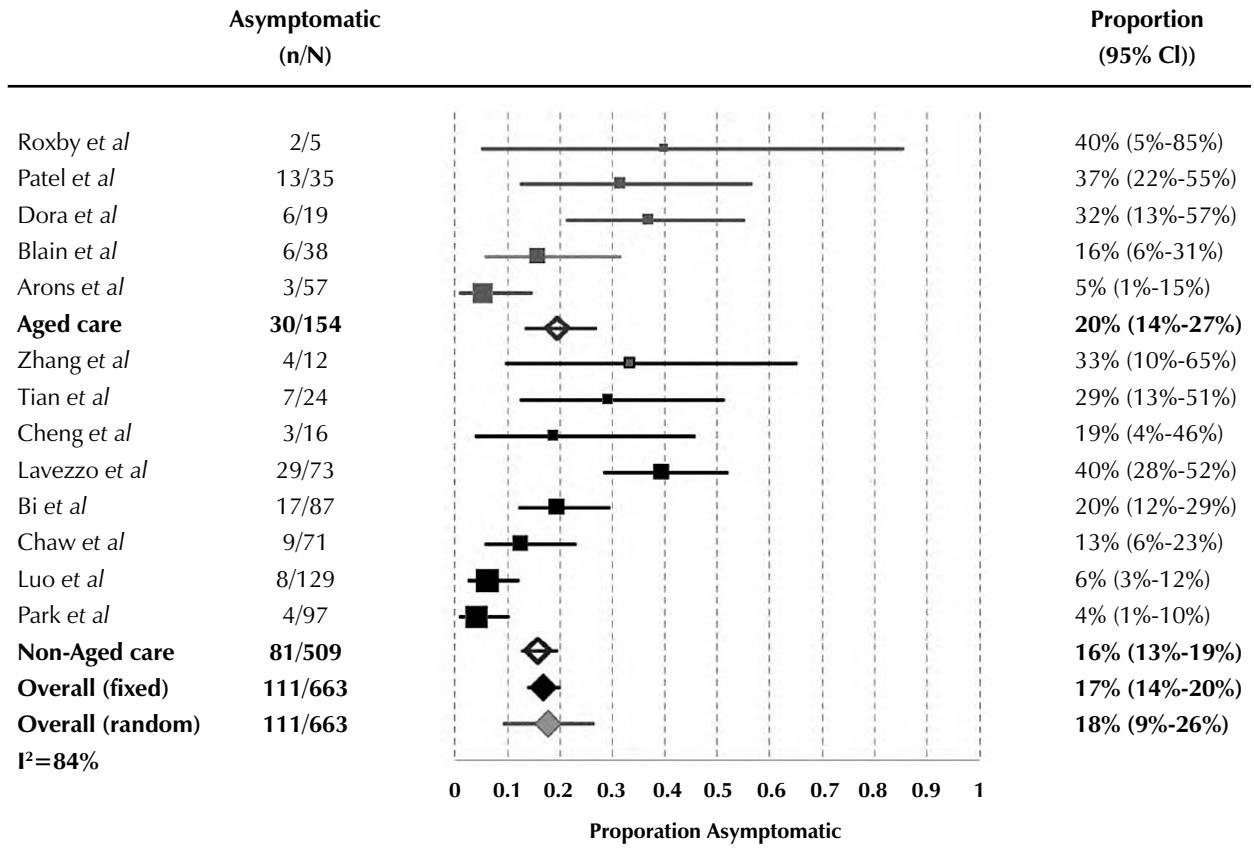
**Figure 3: Pooled estimates of proportion of asymptomatic carriers by subpopulations**
***N = Positive cases; n = Asymptomatic cases***




The demographic characteristics **(Table 1)** indicate that most of the tested individuals were adults, with a mean age of more than 75 years in the five SNF studies and a mean age of more than 31 years in the non-aged care studies. The proportions of children and young people (0-20 years) ranged from 6% to 23.5%.

Diagnosis in all studies was confirmed via RT-PCR and in two cases was supplemented with radiological evidence [17, 21]. Testing of individuals in the study sample varied across settings but was generally very high: all contacts regardless of symptoms [11, 13, 14, 17, 18, 21], more than 97% of SNF residents [10, 12, 15, 19, 20], and 85.9% of an entire town [16]. The length of follow-up for monitored individuals in the SNF studies ranged from seven to 30 days [10, 12, 15, 19, 20]; 14 days for the Bruneian [13], Taiwanese [14], Korean [18], and Chinese close contacts [17, 22]; seven to 14 days in the Italian community [16]; 12 days for 95% of all contacts in the Shenzhen community surveillance [11]; and a mean of 16 (SD 6) days in Liaocheng, China [21].

The proportion of asymptomatic cases in the 13 included studies ranged from 4% (95% CI 1% to 10%) in Korea [18] to 40% in Vò, Italy [16] and in an aged care facility in the United States [20]. Combining data from all 13 studies, we estimate that 17% of cases were asymptomatic (fixed effects 95% CI 14% to 20%;); for the eight non-aged care studies, 16% (95% CI 13% to 19%); and for the five studies of SNFs, 20% (95% CI 14% to 27%) **(Figure 3)**. The corresponding estimated proportions in the random-effects meta-analysis were, overall, 18% (95% CI 9% to 26%); non-aged care, 16% (95% CI 7% to 26%); and aged care, 21% (95% CI 5% to 36%). The 95% prediction interval was 4% to 52%. In the sensitivity analysis, which omitted studies in which length of follow-up was less than 14 days [10, 11, 16, 20], the overall estimate was modestly lower at 15% (fixed-effects 95% CI 12% to 18%) or 17% (random-effects 95% CI 8 to 26%). Heterogeneity as expressed by *I*2 was 84%.

Five studies reported data on secondary infection transmission from asymptomatic cases **(Table 2)**. The asymptomatic transmission rates ranged from none to 2.2%, whereas symptomatic transmission rates ranged between 0.8% and 15.4%. Cycle threshold from real-time RT-PCR assays or the viral load did not differ between asymptomatic and symptomatic individuals in three of the studies [10, 14, 16]. Overall, the RR of asymptomatic transmission was 42% lower than that of symptomatic transmission (pooled RR 0.58, fixed-effects 95% CI 0.335 to 0.994, p = 0.047; RR 0.38, random-effects 95% CI 0.13 to 1.083, p = 0.07; *I*2 = 43.4%).

**TABLE 3: Risk of bias in 13 included studies***

| | *Risk-of-bias assessment questions* | | | | |
|---|---|---|---|---|---|
| **Included Studies** | 1. Was the sampling frame a true or close representation of the target population? | 2. Was the likelihood of non-response bias among those at risk of infection minimal? | 3. Is the reference standard used likely to correctly classify all SARS-CoV-2 infections? | 4. Was an acceptable case definition used in the study? | 5. Was the length of follow-up to define case definition appropriate? |
| Roxby *et al* | ☺ | ☺ | ☺ | 😐 | ☺ |
| Patel *et al* | ☺ | ☺ | ☺ | 😐 | ☺ |
| Dora *et al* | ☺ | ☺ | ☺ | 😐 | ☺ |
| Blain *et al* | ☺ | ☺ | ☺ | 😐 | ☺ |
| Arons *et al* | ☺ | ☺ | ☺ | 😐 | ☺ |
| Zhang *et al* | ☺ | ☺ | ☺ | ☺ | ☺ |
| Tian *et al* | ☺ | ☺ | 😐 | 😐 | ☺ |
| Chen *et al* | ☺ | ☺ | 😐 | 😐 | ☺ |
| Lavezzo *et al* | ☺ | 😐 | ☺ | 😐 | ☺ |
| Bi *et al* | ☺ | 😐 | 😐 | 😐 | ☺ |
| Chaw *et al* | ☺ | ☺ | 😐 | ☺ | ☺ |
| Luo *et al* | ☺ | ☺ | ☺ | ☺ | ☺ |
| Park *et al* | ☺ | ☺ | ☺ | ☺ | ☺ |

*SARS-CoV-2 = Severe acute respiratory syndrome coronavirus 2; Green smiley face = Low risk; Yellow straight face = moderate or unclear risk*

### Risk of bias of included studies

**Table 3** summarizes the overall risk-of-bias assessment of the nine included studies (the full list of risk-of-bias questions is in Supplemental Appendix 3). All of the studies were evaluated as low risk of bias for the sampling frame and length of follow-up domains (domains 1 and 5), which were part of the inclusion criteria. Two studies had potential non-response bias because not all of the eligible participants were tested (14% [463/3,275] of the target population was not tested in the Lavezzo *et al* study [16] or results were not reported for all tested participants (87/98 cases were reported in the Bi *et al* study [11]; domain 2). Four studies either had not tested the study population at least twice during the follow-up period or had not provided clear information on testing [11, 13, 14, 21] (domain 3). Nine studies did not explicitly state the asymptomatic case definition they adhered to or had additional bias because of a high percentage of people in the SNFs with severe cognitive impairment [10–12, 14–16, 19-21] (domain 4).

### Excluded studies

Several well-publicized studies did not meet our inclusion criteria. The outbreak on the Diamond Princess cruise ship involved 3,711 passengers, of whom more than 600 acquired COVID-19 [3]. Many of the positive cases were relocated to medical facilities in Japan without details of their clinical progression. To correct for the lack of follow-up, Mizumoto *et al* applied a statistical adjustment for the right censoring and estimated that 17.9% (95% CI 15.5% to 20.2%) of positive cases were asymptomatic.

An open-invitation screening of the Icelandic population suggested that around 0.8% of the population were SARS-CoV-2 positive, with half classified as (initially) asymptomatic [2]. However, because there was no follow-up, we cannot separate asymptomatic from pre-symptomatic individuals. Moreover, the study excluded symptomatic people undergoing targeted testing, which impeded estimation of an overall asymptomatic rate.

A study of 215 pregnant women in New York identified 33 SARS-CoV-2–positive women [23]. On admission to the delivery unit, four of the 33 positive cases were symptomatic and three became symptomatic before postpartum discharge, suggesting an asymptomatic rate of 79% (26/33). However, the two days of follow-up were insufficient to meet our inclusion criteria.

A case report of a pre-symptomatic Chinese businessman transmitting COVID-19 to a German business partner was also excluded because despite three other people acquiring the infection from the infected German source, none of them was asymptomatic at follow-up [24]. A five-day point-prevalence testing of adults living in homeless shelters in Boston found 147 positive cases, of which the majority had mild or no symptoms [25]. We excluded this study because no numeric estimate was included of those who were truly asymptomatic, and there was no follow-up assessment.

Two studies examined people repatriated from overseas to their home countries by plane. Neither study was clear on whether symptomatic people could board the plane and be included, and if they were excluded, the asymptomatic rates would be overestimated. A study of 565 Japanese citizens repatriated from China [26] found 13 positives – four asymptomatic and nine symptomatic, based on screening on arrival. Another study of 383 Greek citizens repatriated from the United Kingdom, Spain, and Turkey [27] found 40 asymptomatic positive people on arrival, four of whom later self-reported symptoms. Again, the likely initial exclusion of symptomatic people and the lack of comprehensive follow-up would both result in overestimation of the asymptomatic rates.

## DISCUSSION

### Principal findings

Although the rate of asymptomatic COVID-19 cases has received considerable attention, we found only 13 studies that provided an adequate sample frame and follow-up to ascertain a valid estimate of the proportion of asymptomatic cases. The combined estimate of the asymptomatic proportion was 17% (95% CI 14% to 20%) but had considerable heterogeneity ($I2$ = 84%) and a 95% prediction interval that ranged from 4% to 52%.



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There was no clear difference in the proportions between aged care and non-aged care studies. Only five of the 13 studies provided data on transmission rates from asymptomatic cases. The transmission risk from asymptomatic cases appeared to be lower than that of symptomatic cases, but there was considerable uncertainty in the extent of this (RR 0.58; 95% CI 0.335 to 0.994, $p = 0.047$).

**Strengths and weaknesses of the study**

Strengths of our systematic review include achieving full methodological rigor within a much shorter time frame than traditional reviews using enhanced processes and automation tools [5]. We also critically assessed the risk of bias of all full-text articles we screened to include studies with the least risk of bias in sampling frame and length of follow-up domains to be able to differentiate between asymptomatic and pre-symptomatic cases.

Our findings have several limitations. First, our search focused on published and pre-print articles, and we may have missed some public health reports that are either unpublished or only available on organizational websites. Second, the design and reporting of most of the studies had a number of important deficits that could affect their inclusion or our estimates. These deficits include poor reporting of the sample frame, testing and symptom check, and follow-up processes. Such reporting would have been considerably aided by including a flow chart of cases (as Lavezzo *et al* [16] did) with identification, testing, and follow-up, including missing data. A further important limitation was the poor reporting of symptoms, which was often simply dichotomized into symptomatic versus asymptomatic without clear definitions and details of possible mild symptoms. The included studies did not report sufficient data to examine the impact of age and underlying comorbidities on the asymptomatic rate. Finally, all included studies relied on RT-qPCR; hence, some cases might have been missed because of false-negative results, especially when study participants were only tested once [28]. If the tests missed more asymptomatic cases, then the true proportion of asymptomatic cases could be higher than our estimates. However, false-positive results, which may occur when people without symptoms are tested in low-prevalence settings, would mean the true prevalence of asymptomatic cases was lower than our estimates.

**Strengths and weaknesses compared with other studies**

Several other non-systematic and systematic reviews have examined the proportion of asymptomatic cases. The non-systematic reviews estimated asymptomatic rates as between 5% and 80% [4, 29]. However, they included only early cross-sectional reports and did not critically appraise the study design, nor did they attempt to pool the most valid studies. Five other systematic reviews reported pooled estimates of asymptomatic rate as between 8% and 16% [30–34]. However, these reviews included studies that we excluded because of high risk of bias in the sampling frame. Ongoing monitoring for new studies is warranted but should include robust methodological assessment, including ensuring included studies have a sufficient follow-up period to differentiate the asymptomatic from the pre-symptomatic cases. Our review currently also has a more recent search date than other reviews and includes sensitivity analysis by length of follow-up time. Our estimate of risk of transmission by asymptomatic cases was comparable to those reported in two other empirical reviews by Buitrago-Garcia et al (RR 0.35) and Koh *et al* (RR 0.39) [32, 34].

**Meaning of the study**

Estimates of the proportion of the cases that are asymptomatic and the risk of transmission are vital parameters for modelling studies. Our estimates of the proportion of asymptomatic cases and their risk of transmission suggest that asymptomatic spread is unlikely to be a major driver of clusters or community transmission of infection, but the extent of transmission risk for pre-symptomatic and minor symptomatic cases remains unknown. The generalisability of the overall estimate is unclear, and we observed considerable variation across the included studies, which had different settings, countries, and study design, reflected in the reasonably wide prediction interval.

**Unanswered questions and future research**

Many unanswered questions about asymptomatic cases remain. Only one of the more recent studies we included tested patients for immunoglobulin G antibodies to determine seroconversion among elderly individuals. Without repeated and widespread RT-PCR and antibody tests, it is difficult to accurately estimate the prevalence of COVID-19 infection and inform our infection prevention strategies [35]. The role of viral load and virus shedding dynamics in asymptomatic and symptomatic cases will further help answer the question of forward transmission and disease length and severity. Other unknowns include whether there is a difference in the proportion of cases that are asymptomatic according to age (particularly children versus adults), sex, or underlying comorbidities, and whether asymptomatic cases develop long-term immunity to new infections. For most studies, the PCR (positive) cases were traced from the index cases, and the testing was carried out mostly at the beginning of the pandemic wave for the locale. So, for this review of inception cohorts, people with long-term persistent positive testing were unlikely to be misclassified as asymptomatic. The issue of persistent PCR positivity after a person has recovered from infection might be of concern to more recent studies conducted at some time after the first wave of the pandemic. In such studies, researchers will need to ask about history of illness compatible with COVID-19 even if this occurred months ago, and PCR testing could be supplemented by other tests such as viral culture and anti-SARS-CoV-2 antibody tests.

Our recommendations for future research also include improved clearer reporting of methods, sampling frames, case definition of *asymptomatic*, extent of contact tracing, duration of follow-up periods, presentation of age distribution of asymptomatic cases, and separation of pre-symptomatic and mild cases from asymptomatic cases in results tables. Most studies used a limited definition of asymptomatic COVID-19 case, which could lead to mixing paucisymptomatic cases with asymptomatic cases. If that were a common issue, then the true prevalence of asymptomatic cases would be even lower than the current estimates. A reliable estimate of the proportion of asymptomatic

cases and the burden of disease is imperative in understanding the infection transmission capacity of asymptomatic cases to inform public health measures for these individuals who, according to our findings, appear to pose lower risk of transmission. Until we have further immunological and epidemiological evidence, we advise that the importance of asymptomatic cases for driving the spread of pandemic to be considered with caution.

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# Intra and interspecies interaction between mass confined animals and their handlers – an ideal reservoir for Coronavirus evolution

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Multiple variants of the virus responsible for COVID-19 have been detected since the pandemic started, however a miniscule minority succeed in persisting and successfully promulgating infection in humans. A research group in Basel, Switzerland has detected a persistent mutant designated as 20A.EU1 of COVID-19, which has spread extensively in the European Continent [1]. The initial stages of the variant appear to have originated in the North East region of Spain and two outbreaks of infection with this variant were detected in farmers coming from the provinces of Aragon and Catalonia in late June 2020. Later in July, more than 100,000 minks in the Spanish North East were culled as they were found to be infected by SARS-CoV-2 [2]. There is the possibility that the mass confinement of infected animals resulted in high viral reproduction rates increasing the risk for the development of mutants, which through crossing-over and natural selection persisted to become pathogenic in humans.

Spain, following Italy, was one of the first European countries to have witnessed a significant impact of the coronavirus pandemic. The first Italian residents noted to have contracted SARS-CoV-2 infection were in a small town near Milan on February 21, 2020. It was suggested that a super spreader event occurred when a well-attended (about 50,000 spectators) football match between the Spanish team of Valencia and the Italian team of Atalanta was played in the stadium of Bergamo on February 19, 2020. Unknowingly in February, Bergamo was already the focus for seeding COVID-19 throughout the Lombardy region of Northern Italy. Following Italy, not unexpectedly, coronavirus made its appearance in Valencia and the rest of Spain was plunged into lockdown as the pandemic engulfed the whole nation, leading to high mortality rates in the elderly and other vulnerable populations [3].

By July 2020, the COVID-19 mutant Clade G (D614G) was already displacing the original Wuhan1 (Clade D) in most countries, and was prevalent in Spain [4]. This variant may have originally infected the Aragonese and Catalan farmers who possibly transmitted the virus to the mink population in the North Eastern regions of Spain. Similar to humans, where population density is a risk factor for high COVID-19 infection rates, the mass confinement of minks led to widespread infection of the caged animals. This undoubtedly led to a high reproduction number ($R_o$) in the confined animal population due to the exponential infection rate. High reproduction rates are a prerequisite for the occurrence of mutations, which eventually may thrive due to adapting to natural selective pressures [5]. In the event of the high reproduction rate and elevated viral counts, the possibility of viable mutations transmissible to humans could be more probable in the infected confined mink population. The risk is further exacerbated, similar to a multiplier effect, as repeated interspecies' infection may occur between the confined animals and their human handlers.

Following high mortality rates, national lockdown was enforced in mid-March 2020 in both Italy and Spain [6], and social distancing efforts helped in reducing the $R_o$ by May 2020, which subsequently caused the diminution of restrictions in June. From the month of June 2020, with travel restrictions relaxed, tourists in their thousands crowded the Spanish coastal resorts. The holiday mood may have caused the relaxation of restriction on social distancing and the requirement of mandatory face protection. It should be noted that particulate matter and aerosol exhalation have been suggested as vectors for SARS-CoV-2 [7, 8], and the presence of vaping-derived particulate matter commonly performed in Spain [9] as a practice to reduce tobacco smoking, may have enhanced the transmission of the 20A.EU1 variant throughout the Spanish peninsula, and later to the European Continent. Due to the paucity of transatlantic travel, the 20A.EU1 variant has not yet been detected in the Americas.

Finally, the notion that some animals are reservoirs for coronaviruses is not a novel one. Bats and the Formosan pangolin were thought to have harboured the SARS-CoV-2 virus, which was transmitted to humans and further genetic studies indicate that SARS-CoV-2 shares 91.02% genomic concurrence with the Pangolin-CoV and Pangolin-CoV shares 90.55% genetic similarities with the BatCoV RaTG13 [10]. Although bats are increasingly recognized as the primary reservoir of coronaviruses due to the similarity in the crucial receptor binding domain between the Pangolin-CoV and SARS-CoV-2, other reports suggest the Formosan Pangolin

could be the principal reservoir [11]. The risk of transmission is elevated when animals are caged in large numbers. The forced confinement encourages high viral reproduction rates which may then increase the probability of viable pathogenic mutations.

Our hypothesis that mass confinement of minks in Spain is associated with the development and spread of the 20A.EU1 variant in the European continent needs to be investigated further. Besides the risk of coronavirus mutation and the potential low efficacy to vaccines, there is also the element of animal cruelty associated with mass confinement.

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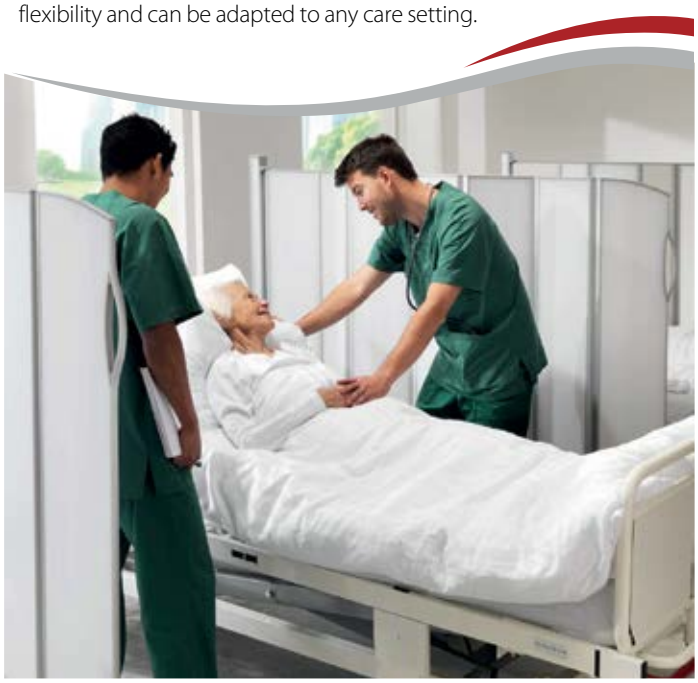

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# The HEINE Reusable Laryngoscope System

## Featuring the EasyClean LED Handle and HEINE Classic+ Blades

**Most Environmentally Friendly Solution:** No plastics in product design unlike disposables.

**100% Waterproof:** Handle is sealed so you can scrub it, wash it, soak it. Do not worry about excessive moisture from wipes corroding the inside of your handles.

**Wipe-Down Compatible Handle:** VALIDATED IFU Hygienic Reprocessing Document for low level surface disinfection of your handles.

**Sterrad \ Steris Compatible:** The only LED Handle with a VALIDATED IFU Hygienic Reprocessing Document for low-temp gas plasma sterilization with ZERO disassembly. Do not worry about pieces getting lost or broken.

**Safe for Patients:** One piece metal design results in easy reprocessing.

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**Experience our comfortable and skin-friendlier glove solutions with PI KARE™ Technology to know the difference.**

References: **1.** Higgins C, Palmer A, Cahill J, Nixon R. Occupational skin disease among Australian healthcare workers: a retrospective analysis from an occupational dermatology clinic, 1993-2014. Contact Dermatitis. 2016;75(4):213-22 **2.** Heese A, Hintzenstern JV, Peters K, Koch HU, Hornstein OP. 1991. Allergic and irritant reactions to rubber gloves in medical health services. Journal of the American Academy of Dermatology. 25:831-839.

PI-KARE™
Skin-friendly PI Technology

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## 3-5 minutes

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## Always connected

IoT-enabled for instant analysis and reporting

Disinfection is more critical than ever. Visit solarislyt.com to learn how Lytbot can enhance your facility's infection prevention strategy.

1. Lo et al., Disinfection Efficiency Study of a Pulsed Light System, Mount Sinai Hospital, April 1, 2016.
2. Zargar et al., Assessment of LYTBOT to reduce pathogens on nonporous and porous surfaces: Testing with Human Respiratory Coronavirus 229E (ATCC VR-740), CREM Co. Labs, December 11, 2020. (Testing Organism: Human Respiratory Coronavirus 229E (ATCC VR-740). Host: MRC-5 cells (ATCC CCL-171))

Book your Lytbot demo today at solarislyt.com/demo

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