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GloveCare: a pilot study in preparation for a cluster crossover randomized controlled trial of non-sterile glove-based care in preventing late-onset infection in the NICU

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Abstract

Background Late-onset infections (LOI) are a major cause of morbidity and mortality among patients in the neonatal intensive care unit (NICU). Gloving after hand hygiene may be a pragmatic approach to prevent infections that arise when healthcare workers' hands transmit pathogens to neonates.

Objective To determine the feasibility of conducting a multicenter, open-labeled randomized controlled trial (RCT) to determine whether a protocol that requires healthcare workers (HCWs) in a level 3 NICU to wear non-sterile gloves plus hand hygiene reduces the occurrence of a late-onset infection, compared to hand hygiene alone.

Methods In this single-center pilot study, we recruited neonates admitted to the McMaster Children's Hospital NICU from June 2017 to May 2018. The NICU was randomized to begin with the standard (control) arm for 6 months (June 2017 to Dec 2017), followed by the gloving (GloveCare) arm for 6 months (Jan 2018 to July 2018), with a 2-week washout period in-between to educate healthcare workers about gloving. We measured numerous feasibility outcomes including enrollment, event rate, and compliance with hand hygiene (Moment 1: before patient contact, Moment 2: before clean procedure, Moment 3: after body fluid contact, Moment 4: after patient contact) and gloving compliance.

Results We enrolled 750 neonates (390 Standard care, 360 GloveCare) and achieved 100% enrollment. We found higher hand hygiene compliance during the standard care arm compared to the GloveCare for all four moments of hand hygiene (Moment 1: 87% vs 79%, OR=1.86 (1.34, 2.59); Moment 2: OR=1.73 (1.00, 3.01); Moment 3: OR=1.11 (0.62, 1.98); Moment 4: OR=1.65 (1.27, 2.14)). We developed and validated a method to calculate glove compliance, which ranged from 48 to 85%, and was highest for moment 3 (doffing after a procedure or body fluid exposure risk). No adverse events were documented for patients or staff.

Discussion Reduction in hand hygiene compliance in the GloveCare arm presents a pragmatic challenge in ascertaining the effectiveness of gloving to prevent LOI. Most LOIs were non-sterile-site infections, which is considered a less patient-important or clinically relevant outcome compared to sterile-site LOI. Ensuring efficient collection and validation of hand hygiene and gloving data is imperative.

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Conclusion The pilot study demonstrated the feasibility of this intervention though modifications to improve hand hygiene compliance during GloveCare will be important prior to a multicenter cluster RCT to assess the efficacy of non-sterile glove-based care in preventing LOI in the NICU.

Trial registration Clinicaltrials.gov, [NCT03078335](https://clinicaltrials.gov/ct2/show/study/NCT03078335)

Keywords Late-onset infection, Nonsterile gloves, Neonatal intensive care unit

Key messages regarding feasibility

- What uncertainties existed regarding the feasibility?

The feasibility of implementing, sustaining, and measuring compliance with glove-based care has not been studied in a systematic way before. In order to roll this intervention out in the multicenter-based trial required to demonstrate a difference in late-onset infection, the feasibility of implementing this intervention is critical to the fidelity of a future pragmatic trial.

- What are the key feasibility findings?
Our participant enrollment (target >90%) feasibility outcome was met through the use of waiver of consent and an opt-out of data collection option. We did not achieve our target of 90% hand hygiene or 90% gloving compliance for any moment except moment 1 in the standard arm. Within the GloveCare arm, hand hygiene compliance was higher compared to glove compliance in Moment 1. In comparison, glove compliance was higher for Moments 2, 3, and 4 than hand hygiene compliance in the GloveCare arm. This indicates the need for modifications to improve compliance with both hand hygiene and gloving in both arms prior to a multicenter study.
- What are the implications of the feasibility findings for the design of the main study?
We have validated a methodology for glove compliance metrics for a future study. We were also able to establish the event rate of 10%, which will be used to inform the sample size calculation for a future trial, and consider narrowing to the most appropriate patient population with the NICU for this intervention.

Introduction

Late-onset infection (LOI, defined as infection after 72 h of age) is a serious cause of long-term morbidity and mortality among patients in the neonatal intensive care unit (NICU). As healthcare worker hands are the most common vehicle for transmission of pathogenic organisms to neonates [1], hand hygiene is reported as the most important infection control practice for preventing

cross-transmission of microorganisms [2–4]. However, hand hygiene compliance rates in the literature vary immensely (from 5 to 89% [5]) and hand hygiene strategies alone have not shown an association with reduced bloodstream infection rates [6, 7]. Clinically relevant bacteria remain on health care providers' hands despite hand hygiene [8]. This suggests another barrier, such as non-sterile gloves, may be important to prevent infection.

A proactive approach to prevent, rather than treat LOI, with the risk of neurodevelopmental impairment and antimicrobial resistance, decreases the length of hospital stay and costs of care [9–11]. Adherence to infection control practices in the NICU is fundamental to reduce late-onset infection [12]. Implementation of infection control bundles over 15 years has significantly reduced NICU LOI rates [13]. The primary components of these infection control bundles include collaborative team-based education, central line insertion bundles, and hand hygiene promotion; these are already standard of care in most NICUs [13–17].

The addition of non-sterile glove-based care to standard infection control practices including hand hygiene has been explored. One randomized controlled trial (RCT) demonstrated a significant reduction in gram-positive bloodstream infections in neonates randomized to the non-sterile glove use arm [18]. Additionally, two retrospective studies demonstrated a significant reduction of LOI with non-sterile glove use. Ng et al. demonstrated a nearly 3-fold reduction in late-onset bloodstream infections in preterm infants with gloving compared to conventional hand hygiene alone [6]; however, other practice changes in infection control may have been a confounding factor. Another retrospective cohort in late preterm infants (32–36 weeks gestational age) found 6 episodes of late-onset clinical infection in 111 patients in the standard arm (2.99/1000 hospital days), compared to zero episodes in 89 patients in the gloving arm, with no difference in culture-positive bloodstream infections (2 vs. 0) between groups [19]; however, this study was limited by its small sample size and use of “clinically diagnosed” sepsis. Kaufman et al. had previously published an individually randomized control trial (RCT) which demonstrate a significant reduction in gram-positive bloodstream infections, and fewer central line infections indicating the importance of skin flora as pathogens for neonates.

A key knowledge gap remains in understanding the effectiveness of gloving in preventing both sterile site (e.g., bloodstream) and non-sterile site (e.g., pneumonia) LOI, across various gestational ages and birth weights. In addition, in many of the referenced studies, gloving compliance was rarely reported and/or compared to hand hygiene compliance. Thus, we sought to first determine the feasibility of conducting a multicentre RCT to determine whether glove-based care (in addition to hand hygiene) would reduce LOI in the NICU, as compared to standard care. The objective of our pilot RCT was to assess feasibility outcomes including participant enrolment, hand hygiene compliance, compliance to gloving, and LOI prevalence and rate, to assess if a pragmatic multicentre cluster RCT could be conducted. Additional outcomes include the types of LOI pathogens detected, additional prevalence of patients who had additional precautions (isolation), the LOI adjudication process, and qualitative description of the auditing verification process.

Materials/patients and methods

This pilot was a single-center study comprising two groups of infants, each recruited sequentially over two separate time periods to receive standard hand hygiene care (Arm 1) or glove-based care (Arm 2) in preparation for a multi-center cluster-crossover trial which will randomize entire sites (clusters) to the two arms and then crossover to the other arm after a period of time. The pilot was conducted in the NICU at McMaster Children's Hospital (MCH) in Hamilton, Canada, between June 2017 and June 2018. The protocol was registered at www.clinicaltrials.gov (NCT03078335).

Ethics

The study was approved by the Hamilton Integrated Research Ethics Board (#2175). A waiver of consent process was used as the intervention was considered a minimal risk (per The Interagency Advisory Panel on Research Ethics 2) and the study would not have been feasible without unit-wide standardization of infection prevention and control (IPAC) practices. Bedside nursing staff informed and provided an information sheet to parents about the change in IPAC policy in the NICU for the study duration. Parents had the option to withdraw from data collection within the study, but were cared for based on the arm of randomization during the neonates' admission. Due to the minimal risk of the intervention itself, no trial-stopping rules or interim analyses were planned.

Study population and setting/inclusion and exclusion criteria

Infants admitted to the MCH Level 3 NICU for a minimum of 2 days were included in the study for their duration of stay. Any infection outcomes that occurred in infants requiring droplet and/or additional precautions for infection control reasons were excluded from analysis (as this involved glove use for reasons unrelated to the study intervention) as established a priori. Infection outcomes in patients transferred in and out of the NICU from other centers were included for their duration within our facility (events occurring within the first 48h after transfer to our NICU were excluded as they could be attributed to the transferring facility). Any events within 48 h after discharge were not collected as we did not have access to data from external facilities. The MCH NICU hand hygiene compliance prior to the study exceeded the 90% target for moments 1 and 4. Gloves of different sizes and alcohol-based hand rub were available at each bedside and hand hygiene sinks were located in proximity to all bedsides. Per unit standards, upon entry to the NICU, all health care providers were required to scrub to the elbows and there was a "bare below the elbows" policy in the NICU.

Study design

This single-center randomized pilot study was conducted to evaluate the feasibility of a future multicenter cluster-crossover randomized trial. This pilot study had 2 intervention periods lasting 6 months each, with a 2-week washout period in between. The 2-week washout period ensured provider education was adequately delivered and minimized contamination of neonates that were cared for in both arms of the study. The NICU was randomized using a computer simple randomization sequence (operationalized by an independent statistician) resulting in the standard arm being selected for the first 6-month period, followed by the GloveCare arm. Due to the pragmatic nature of the trial, other clinical practice changes that occurred during the study year were monitored but not deferred. The use of probiotics was introduced as an accepted standard of care in the NICU at the end of the standard arm for necrotizing enterocolitis prevention ([Appendix 1](#)). No other major known confounders or infection control/clinical practice changes occurred during the study. The study was open label as health care workers could not be blinded to the treatment assignment.

Definition of late-onset infection

Late-onset infection episodes were categorized: sterile-site LOI (i.e., culture-positive meningitis, bacteremia, urinary tract infection) and non-sterile-site LOI

(culture-negative meningitis, single blood culture positive with coagulase-negative staphylococci, abdominal infection, pneumonia, clinically diagnosed cellulitis, and “culture-negative” sepsis). See [Appendix 2](#) for further details of infection definitions. We also collected C-reactive protein (CRP) measurements and time to the first infection.

Prior to intervention (standard arm)

Healthcare workers provided standard care, namely hand hygiene before all patient, bed space, and intravenous catheter contact. Information sessions were offered to all clinical staff to review hand hygiene best practices, appropriate glove selection, donning and doffing procedures, and skin care. These sessions occurred prior to study commencement to ensure front-line clinician buy-in to the process/study. During the standard arm, gloves remained accessible to staff as per standard of care, and staff continued to use gloves as they deemed necessary (e.g., prior to contact with body fluids).

Study intervention period (GloveCare arm)

Refresher educational information sessions (as above) were held again prior to commencing the GloveCare arm ([Appendix 3](#)). During the study period, all healthcare workers in the NICU were instructed to wear non-sterile gloves, after routine hand hygiene, for all patient and line contact (GloveCare). Health care providers included any hospital staff providing hands-on care. Multi-disciplinary consultation occurred prior to study commencement to ensure staff were aware of the study, to stress the importance of hand hygiene even during the GloveCare period, and increased auditing measures. During these sessions, strategies to optimize ability to glove during care were discussed. It was also emphasized *a priori* that patient care needs took precedence over the need to don gloves in emergent situations. Patient contact was defined as any contact with the patient or the patient environment (i.e., cot/incubator and any equipment attached to the patient). Intravenous catheter contact was defined as contact with central or peripheral catheters, including making or breaking a connection with the line. Signage and study logos were posted to remind care providers of the GloveCare intervention, as well as the study logo visible at the entrances to the incubators or cots ([Appendix 4](#)). Staff were asked to self-report any missed gloving opportunities (and the reasons for) on a data collection sheet available at each bedside ([Appendix 4](#)). Parents and caregivers were not included in the GloveCare intervention. While it is recognized that parents may contribute to the colonization of infants with bacteria that may lead to healthcare-associated infections, they were not required to wear gloves because (1) skin to skin contact is considered a critical part of bonding for infants and

parents [20], (2) parents provide less hands-on contact with invasive devices, (3) parents are less likely colonized with pathogenic flora [21], and (4) normalization of household bacterial flora is recognized as an important part of the diversification and maturation of the neonatal microbiome [22, 23].

Feasibility outcomes included:

- *Participant enrollment* (target >90% enrollment (e.g., do not sign the opt out of data collection waiver))
- *Hand hygiene compliance* for moments 1 to 4 (target >90% compliance based on weekly randomized audits for moment 1 and moment 4) (moments are defined below)
- *Glove use compliance* during the GloveCare arm (with a target of >90%). The hand hygiene target is higher than the overall hospital-wide hand hygiene target of 80%.

Hand hygiene and glove compliance

Compliance with hand hygiene was monitored by auditors three times weekly as per a randomized schedule in both study arms. Hand hygiene is an integral part of care, regardless of the use of gloves. Audits were for a minimum of 1 h, either during day or night shifts (day shift: 7am to 7pm, night shift: 7pm to 7am) to get a representative sample of clinical care and staff ([Appendix 6](#)). Randomization of monitoring was performed using SAS Software Version 9.3 (Cary, NC, USA). Moments 1 to 4 as defined by Public Health Ontario [24] were audited using licensed Handy Audit® (Version 2.0) software. The results of the hand hygiene and glove compliance audits were relayed back to the NICU on a monthly basis during routine IPAC meetings with the NICU staff to continue to support adherence with study interventions. We also allowed providers to self-report in a separate document when they had a known glove miss during the gloving arm, to understand in what circumstances were providers finding gloving difficult to comply with.

For glove compliance, we defined Moment 1 as donning gloves before touching the patient or their environment, Moment 2 as donning gloves before an aseptic procedure, Moment 3 as doffing gloves after contact with body fluid, and Moment 4 as doffing gloves after touching patient or patient environment. We developed a Python script to measure the four moments of glove compliance from Handy Audit® reports. An infectious disease clinician and hospital hand hygiene coordinator manually assessed the four glove compliance moments for 5% of all audits and compared them to the results of the Python script for validation agreement. From the Python script for validation agreement, we manually removed Moment

3 and 4 glove misses when there was no donning prior; thus, only a Moment 1 miss would be recorded. Overall glove compliance was then calculated from all audits during the glove compliance period. Glove compliance was measured in addition to hand hygiene compliance; staff must perform hand hygiene before donning gloves and after doffing gloves as this is the standard of care.

The primary clinical outcome was *the event rate of LOI*. LOI adjudication was performed to ensure accurate event rates by two independent adjudicators blinded to study arm (SK, KT). The adjudication process included review of the clinical chart including clinical notes, laboratory, and microbiology data. The 6-month duration of each arm in the study was selected as the planned duration for the multicenter trial depending on the event rate of infection episodes during the pilot. Study process outcomes include the adequacy of research resource allocation, research coordinator capacity, processing times for evaluating a potential new event of LOS, time required for adjudication of events, and ensuring the accuracy of hand hygiene compliance data.

Data collection

Data was recorded in an anonymized Research Electronic Data Capture Program (REDCap[®]) database [25]. Information on each neonate including demographics, infection risk factors (i.e., duration of rupture of membranes, prenatal steroid use, mode of delivery, vascular access, ventilatory support, immune-suppressing medications, nutrition), admitting facility, length of stay, and duration of isolation precautions. Infection episodes were collected retrospectively by chart review of all cases that received antibiotics for more than 3 days. Each event was adjudicated by two co-authors blinded to study arm (SK, KT) using a priori determined criteria for infection episodes.

Sample size

As this was a feasibility study, we took a convenience sample of our single site as the sample size. We did not power this study to see a difference in infection rate; however, we did plan for exploratory analysis to assess changes in infection rate based on study arm, recognizing we are not powered to see a difference.

Statistical analysis

Feasibility, clinical, and process outcomes were tabulated and descriptively compared between neonates in the GloveCare and standard arm. Hand hygiene compliance between GloveCare and standard arm was compared using estimated odds ratios accompanied by 95% confidence intervals (CI), and *p*-value calculated through the chi-square test, for all four moments of

hand hygiene. Likewise, we calculated gloving compliance. Other characteristics, including the demographic description of our study participants, the distribution of pathogens, event rate of LOI, and prevalence and duration of additional precautions, were descriptively compared between both arms (Tables 1, 2, and 3). Categorical data is presented as frequency (*n*) and proportion (%) and analyzed using chi-squared tests or Fisher's exact test as appropriate. Continuous data which is normally distributed is presented as mean and standard deviation (SD) as appropriate and analyzed using independent *t*-tests. *P*-values less than 0.05 are considered statistically significant.

Results

Demographic characteristics and recruitment

During the enrollment period (June 5, 2017, to June 1, 2018), 1005 neonates were assessed for eligibility, and 255 were excluded due to short length of stay (less than 3 days) (Fig. 1). We enrolled 390 neonates in the standard arm (June 5, 2017, to November 19, 2017) and 360 neonates in the GloveCare arm (December 4, 2017, to June 1, 2018). Demographic information on the two groups is included in Table 4. There was no statistically significant difference in the prevalence and duration of additional precautions (Table 3). No patients opted out of data collection (Table 5). Probiotics (Florababy[™]) was introduced for necrotizing enterocolitis prevention at the end of the standard arm (Nov 28, 2017).

Hand hygiene and gloving compliance

Hand hygiene compliance in the GloveCare Arm was lower than the standard arm across all moments of hand hygiene, with statistically significant differences seen in Moment 1, Moment 4 overall, and Moment 4 touch patients (Table 6). However, the results should be interpreted with caution; we cannot know which healthcare workers were evaluated at each observation and thus we cannot consider each hand hygiene moment as an independent observation. We did not achieve our target of 90% hand hygiene or 90% gloving compliance for any moment except moment 1 in the standard arm. Within the GloveCare arm, hand hygiene compliance was higher compared to glove compliance in Moment 1. In comparison, glove compliance was higher for Moment 2, 3, and 4 than hand hygiene compliance in the GloveCare arm.

Recruitment was 100% with no families choosing to opt out of data collection. LOI event rate for this study was 10%.

Barriers to gloving compliance

During the GloveCare arm, staff self-reported inability to comply with gloving on 49 occasions, the most common reason documented was having forgotten

Table 1 Pathogen distribution of late-onset infection events

| Number of primary late-onset infection events and mortality | GloveCare arm N=63 | Standard arm N=48 | P-value (chi-square test) |
|-----------------------------------------------------------------------------------------------------------------------------------|-----------------------|----------------------|---------------------------------|
| Sterile site infections, n (%) | | | |
| Any sterile site infection (culture positive meningitis, bacteremia, urinary tract infection) | 14 (22.2) | 15 (31.3) | 0.284 |
| Gram positive | 9 | 7 | 0.965 |
| Gram negative | 9 | 5 | 0.264 |
| Meningitis (n (%)) | 3 (4.8) | 0 (0.0) | 0.257 (FE) |
| Gram-positive | 2 (66.7) | | |
| Gram-negative | 1 (33.3) | | |
| Mean duration of antibiotic therapy (SD) | 29.33 (16.4) | | |
| Mean C-reactive protein (CRP, mg/L) (SD) | 124.25 (72.1) | | |
| Bacteremia (n (%)) | 4 (6.3) | 6 (12.5) | 0.324 (FE) |
| Gram-positive | 3 (75.0) | 0 (0.0) | 0.257 (FE) |
| Gram-negative | 1 (25.0) | 5 (83.3) | 0.0831 (FE) |
| Candida | 0 (0.0) | 1 (16.7) | |
| Mean duration of antibiotic therapy (SD) | 14.25 (9.4) | 30.50 (26.5) | |
| Mean C-reactive protein (CRP, mg/L) (SD) | 81.05 (81.7) | 139.42 (177.0) | |
| Urinary Tract Infection (n (%)) | 7 (11.1) | 9 (18.8) | 0.256 (CS) |
| Gram-positive | 4 (57.1) | 7 (77.8) | 0.203 (FE) |
| Gram-negative | 3 (42.9) | 2 (28.6) | 1.00 (FE) |
| Mean duration of antibiotic therapy (SD) | 9.29 (3.6) | 14.44 (12.3) | |
| Mean C-reactive protein (CRP, mg/L) (SD) | 17.36 (15.7) | 21.70 (14.3) | |
| Nonsterile site infections, n (%) | | | |
| Secondary infection outcomes | 49 (77.8) | 33 (68.8) | 0.284 |
| Culture negative meningitis | 3 (4.8) | 0 (0.0) | 0.257 |
| Mean duration of antibiotic therapy (SD) | 26.67 (16.3) | | |
| Mean C-reactive protein (CRP, mg/L) (SD) | 30.67 (39.2) | | |
| Single positive CONS blood culture (n (%)) | 11 (17.5) | 4 (8.3) | 0.164 |
| Mean duration of antibiotic therapy (SD) | 9.27 (3.3) | 10.50 (4.8) | |
| Mean C-reactive protein (CRP, mg/L) (SD) | 41.42(47.6) | 15.07 (24.1) | |
| Abdominal infection (n (%)) | 4 (6.3) | 7 (14.6) | 0.203 |
| Mean duration of antibiotic therapy (SD) | 14.75 (9.0) | 9.86 (5.2) | |
| Mean C-reactive protein (CRP, mg/L) (SD) | 114.00 (91.5) | 68.91 (93.9) | |
| Pneumonia (n (%)) | 9 (14.3) | 6 (12.5) | 0.785 |
| Mean duration of antibiotic therapy (SD) | 9.89 (1.8) | 10.67 (6.1) | |
| Mean C-reactive protein (CRP, mg/L) (SD) | 34.28 (23.0) | 47.15 (55.1) | |
| Cellulitis (n (%)) | 2 (3.2) | 0 (0.0) | 0.505 |
| Mean duration of antibiotic therapy (SD) | 9 (1.4) | | |
| Mean C-reactive protein (CRP, mg/L) (SD) | 51.60 (17.7) | | |
| Culture negative sepsis (n (%)) | 20 (31.7) | 16 (33.3) | 0.860 |
| Mean duration of antibiotic therapy (SD) | 8.30 (3.4) | 8.75 (2.8) | |
| Mean C-reactive protein (CRP, mg/L) (SD) | 52.04 (43.3) | 47.87 (76.6) | |
| Time to first infection, among all patients with infection, days (n=75), mean (sd) ("Removing" time in additional precautions) | 20.1 (16.1) | 11.4 (8.3) | 0.004 |

FE Fisher's exact test used instead of chi-square

(96%) (Appendix 5, Table 7). Reasons for missed glove opportunities described by staff in informal interviews were that gloves required another step (e.g., de-gloving, hand hygiene, re-gloving); this may have been an

additional barrier to hand hygiene in the GloveCare arm. In some scenarios, staff described that gloving was not possible due to urgent care needs and being unable to delay care to don gloves.

Table 2 Event rate of different infection events

| Clinical measure | GloveCare arm (N=360) | Standard arm (N=390) | Overall (N=750) |
|-----------------------------------------------------------|-----------------------|----------------------|-----------------|
| Total 1 st episode infections (n, %) | 41 (11.4) | 34 (8.7) | 75 (10.0) |
| Sterile site 1 st episode infections (n, %) | 11 (3.1) | 10 (2.6) | 21 (2.8) |
| Nonsterile site 1 st episode infections (n, %) | 30 (8.3) | 24 (6.2) | 54 (7.2) |
| Person-days | 7686 | 7162 | 14848 |
| Number of total episodes | 63 | 48 | 111 |
| Total episodes/1000 person-days | 8.20 | 6.70 | 7.46 |
| Number of sterile-site episodes | 14 | 15 | |
| Sterile-site episodes/1000 person-days | 1.82 | 2.09 | |
| Number of nonsterile-site episodes | 49 | 33 | |
| Nonsterile-site episodes/1000 person-days | 6.38 | 4.61 | |

Table 3 Infants entered into additional isolation precautions

| Additional precautions | GloveCare arm (N= 360) | Standard arm (N=390) | P-value (chi-square) |
|-----------------------------------|------------------------|----------------------|----------------------|
| Once, n (%) | 26 (7.2) | 36 (9.2) | 0.318 (CS) |
| Twice, n (%) | 0 (0.0) | 7 (1.8) | 0.0157 (FE) |
| Thrice, n (%) | 0 (0.0) | 3 (0.8) | 0.140 (FE) |
| Four times, n (%) | 0 (0.0) | 2 (0.5) | 0.270 (FE) |
| Episode 1, mean (sd), median | 18.00 (25.7), 6.50 | 7.75 (15.5), 4.00 | 0.249 |
| Episode 2, mean (sd), median | -- | 0.69 (2.7), 0.00 | |
| Episode 3, mean (sd), median | -- | -- | |
| Episode 4, mean (sd), median | -- | -- | |
| Total duration, mean (sd), median | 18.0 (25.7), 6.5 | 8.4 (15.6), 4.0 | 0.100 |

CS chi-square, FE Fisher's exact

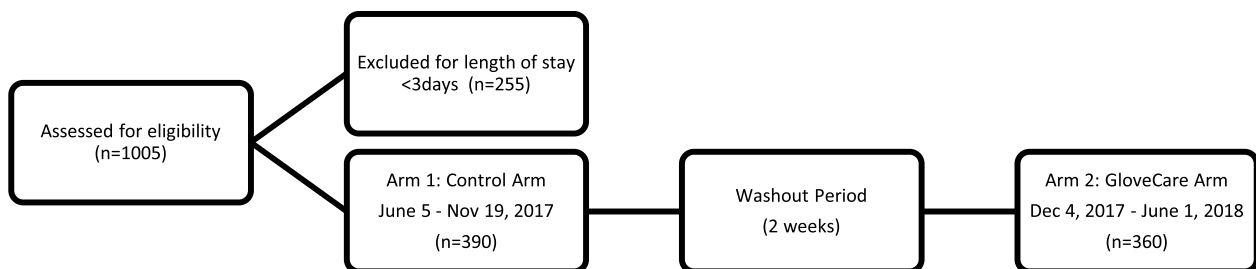


Fig. 1 Flowchart of enrollment, randomization, and analysis

Validation of glove compliance data

While Handy Audit[®] was able to collect when an individual donned or doffed gloves, it was unable to interpret this information into overall glove compliance metrics. Auditing and validating glove compliance data became a feasibility outcome post hoc. We developed a Python[®] script to convert an individual's don and doffing activity into four Moments of glove compliance, similar to hand hygiene. A hand hygiene coordinator and infectious disease clinician iteratively validated the Python script for

over 200 h. Every iteration included manually assessing 5% of all audits and comparing them to glove compliance report from the Python script. Validation of each audit and glove compliance report required a range of 3 to 20 min depending on the complexity of the care provided. Validation was considered complete when there were no discrepancies between the manual auditing and Python script results. Our self-report documentation on glove misses was rarely used and did not provide added value to our compliance data.

Table 4 Study demographic and clinical characteristics

| Demographic and clinical characteristics | GloveCare arm (N=360) | Standard arm (N=390) | P-value |
|-----------------------------------------------------------------------------|-----------------------|----------------------|--------------|
| Male gender, n (%) | 208 (57.8) | 238 (61.0) | 0.365 |
| Gestation at birth (weeks), mean (sd) | 34.11 (4.7) | 34.41 (4.8) | 0.396 |
| Birth weight (grams), mean (sd) | 2332.03 (35.7) | 2452.76 (95.5) | 0.122 |
| Apgar score (1 min), mean (sd) | 6.53 (2.5) | 6.69 (2.4) | 0.375 |
| Apgar score (5 min), mean (sd) | 7.88 (1.7) | 7.94 (1.6) | 0.624 |
| Admitted from | | | 0.369 (FE) |
| Labour and delivery, n (%) | 257 (71.4) | 281 (72.1) | |
| Postpartum ward, n (%) | 6 (1.7) | 11 (2.8) | |
| Community level 2 nursery, n (%) | 93 (25.8) | 97 (24.9) | |
| Home birth, n (%) | 4 (1.1) | 1 (0.3) | |
| Vaginal delivery, n (%) | 168 (46.7) | 177 (45.4) | 0.725 |
| Rupture of membranes (ROM) | | | |
| Ruptured, duration known, n (%) | 351 (97.5) | 388 (99.5) | 0.024 |
| Duration of ROM, mean (sd), among ROM known (glove: n=351; standard: n=388) | 28.93 (132.0) | 36.47 (172.4) | 0.508 |
| Prenatal steroid use (in <34 week), n (%) (N=340) | 118 (71.5) | 131 (74.9) | |
| Risk factors for infection prior to first episode of LOI | | | |
| Central venous line (CVL), n (%) | 156 (43.3) | 168 (43.1) | |
| Peripheral IV access, n (%) | 277 (76.9) | 300 (76.9) | |
| Mechanical ventilation, n (%) | 108 (30.0) | 102 (26.2) | |
| Continuous positive airway pressure (CPAP), n (%) | 212 (58.9) | 263 (67.4) | 0.283 |
| Neonatal steroid (hydrocortisone), n (%) | 19 (5.3) | 26 (6.7) | 0.044 |
| Acid inhibition, n (%) | 17 (4.7) | 27 (6.9) | 0.086 |
| Ventricular shunt, n (%) | 0 (0.0) | 2 (0.5) | 0.373 |
| Surgical PDA ligation, n (%) | 0 (0.0) | 1 (0.3) | 0.487 |
| Total parenteral nutrition (TPN), n (%) | 261 (72.5) | 282 (72.3) | 0.944 |
| Duration of TPN, mean (sd) | 7.76 (13.7) | 7.42 (11.4) | 0.995 |
| Human milk, n (%) | | | 0.241 |
| Only | 143 (39.7) | 180 (46.2) | |
| Any | 173 (48.1) | 173 (44.4) | |
| None | 44 (12.2) | 37 (9.5) | |
| Probiotics, n (%) | 156 (43.3) | 9 (2.3) | 0.015 |
| Length of stay in the NICU, days, mean (sd) (Includes isolation time) | 22.7 (29.1) | 19.1 (25.2) | 0.079 |
| Total duration of isolation, patient-days | 468 | 304 | |

FE Fisher's exact test, used where chi-square tests not doable due to small sample size, ROM rupture of membrane, IV intravenous, CVL central vascular access, CPAP continuous positive airway pressure, PDA patent ductus arteriosus, TPN total parenteral nutrition, NICU neonatal intensive care unit

LOI adjudication process

LOI adjudication was performed to ensure accurate event rates. The process required on average 20 min per case, with a range of 3 to 45 min. The LOI adjudication process excluded 124 LOIs: 6 because they occurred while patients were in additional precautions, 24 because they occurred within the first 3 days of birth (and therefore were early-onset infection), and 94 because they did not meet criteria upon adjudication (e.g., antibiotics discontinued within 48 h).

LOI prevalence and rate

The overall prevalence of first-episode LOI in the entire study period was 10%. There was a LOI prevalence of 11.4% in the GloveCare arm and a prevalence of 8.7% in the standard arm %. The event rate was also higher in the GloveCare group, which showed 8.2 LOI episodes per 1000 person-days compared to the standard group of 6.7 LOI per 1000 person-days [incidence rate ratio = 1.22, 95% CI = (0.84, 1.78), *p*-value=0.293]

Table 5 Primary feasibility outcome

| Outcome | Target | Results |
|----------------------------------------------|----------------------------|---------------------------------------------------------|
| Participant enrolment (N (%)) | >90% | 1005 (100%) |
| Event rate of LOI—number of patients (N (%)) | Not applicable | 75 (10%) |
| Adequacy of resource allocation | 1 FTE Research coordinator | Required extra data entry support |
| Processing time for evaluating new LOS | Not applicable | Estimated at 5 to 30 min depending on complexity of LOI |
| Adjudication of LOS (mean (range)) | Not applicable | 20 minutes per case (3–45 min) |
| Accuracy of data collection | Not applicable | Adjudication resulted in exclusion of 124 LOIs |
| Hand hygiene compliance moment 1 | >90% in both arms | 87.03% in standard arm, 78.28% in GloveCare arm |
| Hand hygiene compliance moment 4 | >90% in both arms | 87.37% in standard arm 80.76% in GloveCare arm |
| Glove compliance moment 1 | >90% in GloveCare arm | 66.2% in GloveCare arm |
| Glove compliance moment 4 | >90% in GloveCare arm | 83.30% in GloveCare arm |

LOI late onset infection, LOS length of stay

Table 6 Hand hygiene and gloving compliance outcomes

| | Hand Hygiene compliance in standard arm—number of HH audits n (%) | Hand hygiene compliance in GloveCare arm—number of HH audits n (%) | Hand hygiene compliance: standard vs GloveCare Odds ratio (95% CI) | P-value | Glove compliance in GloveCare arm n (%), p-value | Compliance in GloveCare arm: hand hygiene vs gloving Odds ratio (95% CI), p-value | P-value |
|------------------------------------|-------------------------------------------------------------------|--------------------------------------------------------------------|--------------------------------------------------------------------|---------|--------------------------------------------------|-----------------------------------------------------------------------------------|---------|
| Moment 1 Total | 510 (87.03) | 346 (78.28) | 1.86 (1.34, 2.59) | <0.001 | 525 (66.20) | 1.83 (1.40, 2.41) | <0.001 |
| Moment 1 touch patient | 266 (90.80) | 194 (80.83) | 2.33 (1.40, 3.89) | <0.001 | 371 (78.60) | 1.14 (0.77, 1.69) | 0.487 |
| Moment 1 Touch patient environment | 244 (83.28) | 152 (75.25) | 1.63 (1.05, 2.55) | 0.028 | 154 (47.98) | 3.30 (2.24, 4.85) | <0.001 |
| Moment 2 | 56 (40.58) | 28 (28.28) | 1.73 (1.00, 3.01) | 0.051 | 75 (52.45) | 0.36 (0.21, 0.62) | <0.001 |
| Moment 3 | 97 (78.86) | 111 (77.08) | 1.11 (0.62, 1.98) | 0.727 | 108 (85.71) | 0.56 (0.30, 1.06) | 0.071 |
| Moment 4 Total^a | 844 (87.37) | 634 (80.76) | 1.65 (1.27, 2.14) | <0.001 | 409 (83.30) | 0.84 (0.63, 1.13) | 0.254 |
| Moment 4 touch patient | 353 (86.31) | 434 (79.49) | 1.63 (1.15, 2.31) | 0.006 | 285 (84.57) | 0.71 (0.49, 1.01) | 0.059 |
| Moment 4 touch patient environment | 286 (84.37) | 312 (84.55) | 0.99 (0.66, 1.48) | 0.945 | 124 (80.52) | 1.06 (0.61, 1.84) | 0.258 |

^a Hand hygiene compliance in GloveCare arm Moment 4 does not add up because touch patient and touch patient environment can be duplicate events

Discussion

This pilot study evaluated the feasibility of the GloveCare in terms of hand hygiene compliance, gloving compliance, adjudication of LOI outcomes, event rate, and resources required to validate compliance data. Overall, this study affirms that GloveCare is a feasible intervention for a multicenter cluster RCT. The results indicated that we must address both hand hygiene and gloving fidelity, and ensure compliance data are collected accurately and efficiently, at the outset of a future multicentre RCT.

We demonstrated recruitment feasibility by exceeding our targeted enrollment rate of 90% and achieved

100% with no families choosing to opt out of data collection. We were able to ascertain the LOI event rate for this NICU at 10% which will greatly inform the sample size calculation for a future multicenter RCT. We will also use the variance observed from the pilot to inform the predictions about the variance in the outcome for the larger trial. This incidence is within the range expected in the literature [6, 18].

The hand hygiene and glove compliance targets of 90% were not achieved for either treatment arm of this study across all four moments and may have been unrealistic targets, based on previous studies by Kaufman et al. (79% hand hygiene compliance) [18] and Baloh et al. (42% hand

hygiene compliance) [26]. Hand hygiene compliance was also markedly lower in the GloveCare arm. This could possibly be due to the belief that hand hygiene is not necessary if donning gloves, despite educating staff about hand hygiene and gloving best practices. Furthermore, if providers perceived each other to be less compliant with hand hygiene while gloving, then they may be more likely to investigate nonspecific symptoms in infants as possible sepsis, thereby leading to a higher event rate of more subjective events (e.g., culture-negative sepsis) during the GloveCare arm. Finally, we identified barriers to gloving through the self-reported tool and staff feedback. This will inform the orientation plan of future studies.

An additional methodologic limitation included the inability to assess if the difference in hand hygiene compliance between treatment arms was statistically significant, due to the absence of data on individual healthcare workers. Consequently, we could not adjust for inadequate hand hygiene as a confounder. A limitation of hand hygiene auditing processes used in most studies is the potential for Hawthorne effect [27, 28], which should falsely elevate compliance rates above true compliance due to visible observers. Other hand hygiene auditing methods include peer auditors, video technology, or validated counts of alcohol-based hand rub uses based on anticipated care environments [29–32]. However, these techniques were not feasible to implement in our setting, due to the resource intensity and patient and provider privacy concerns. We felt that using independent auditing, the gold standard for hand hygiene monitoring, was the optimal approach. We will likely not use any self-report documentation of known misses in gloving given it had poor uptake overall in the pilot.

Secondly, future studies may consider limiting themselves to assessing patients who are low birthweight (i.e., <1500 grams) to gain a higher event rate, and thus, require less sample size for achieving sufficient statistical power. A further challenge for future studies is that while sterile site and nonsterile site infections differ markedly in patient importance, examining them separately would greatly increase the required sample size, as sterile site infections are rare.

Thirdly, validating glove compliance metrics was a time-intensive challenge. Numerous glove compliance scenarios required discussion and consensus between an infectious disease physician and a hand hygiene coordinator. To ease this process, perhaps all possible gloving scenarios and rules should be established prior to script development; this could be incorporated into a future study. A limitation of our validation process is that it relies on Handy Audit[®] results and must be further tested using outputs from other hand hygiene compliance software.

In planning for the future multi-center trial, we will likely pursue a cluster crossover trial so each center

acts as its own control. Our event rate of around 10% was on the lower range of reported late-onset infections which can range between 10 and 30% depending on the gestation ages of the infants. Sample size calculations would likely be based around the lower range given the pragmatic nature of enrolling the entire NICU rather than just the preterm infants would be required. Prior to enrolling centers, we would want to review their relative late-onset infection rates as well to be able to plan for the number of centers required. Our study team felt that a 15% reduction in the incident rate ratio late-onset infection would be clinically significant, and a secondary outcome of delay to time to infection would be another outcome of interest recognizing the highest risk period for NICU infants is their first weeks of life. It will be important to ensure education around hand hygiene for both arms of the study is optimized, and within a multi-center study subgroup analysis among sites with higher and lower hand hygiene compliance may improve our understanding of the impact this has on evaluating the effectiveness of glove based care to prevent LOI.

Conclusion

Our pilot study has demonstrated the feasibility of GloveCare. We have also shown that the feasibility of conducting a multicenter cluster randomized control trial in the future to assess the efficacy of non-sterile gloves to prevent LOI in the NICU is feasible. Additionally, this pilot study demonstrated that a waiver of consent for such studies is a feasible recruitment approach for similar low-risk interventions. Our feasibility target for compliance was not met during this study; however, the pilot study greatly informed the validation required for auditing glove compliance for a future study. Improving hand hygiene compliance efforts in the GloveCare arm will be critical to understand the potential impact of gloves. Lower hand hygiene rates in the GloveCare arm may have inhibited the effectiveness of gloving in reducing infections. Overall, the current pilot study has informed researchers in developing and executing a higher quality future multi-center trial.

Appendix 1

Adjudication criteria and procedure for late onset infection events

Potential events of late-onset infection were flagged in patients admitted to the NICU for more than 2 days with microbiologic clinical cultures collected. Events were adjudicated based on retrospective review of clinical

charts, microbiology, and infection control surveillance hospital epidemiologists.

Late-onset infection events met the following criteria:

- 1) Occurring after 2 days of life to exclude early-onset infection events related to in utero environments or delivery
- 2) Had at least 2 compatible signs and symptoms (including temperature instability, hemodynamic changes, respiratory distress, and increased inflammatory markers (CRP and WBC based on gestation age cut offs [33], change in feeding tolerance, or lethargy as documented by the treating team)
- 3) Had at a minimum; blood cultures sent for analysis
- 4) Antibiotic treatment for more than 4 days to eliminate inclusion of episodes of suspected but not clinically or microbiologically proven infection as no clinically significant infections are treated for <4 days

Late-onset infection episodes were prioritized based on severity, in the following order:

A) Primary outcomes (Sterile-site LOI)


- 1) Culture-positive meningitis
- 2) Bacteremia (positive blood culture, two positive blood cultures for coagulase-negative staphylococci)
- 3) Urinary tract infection (positive urine culture, clinically diagnosed UTI with positive urinalysis (nitrites, leukocytes))

B) Secondary outcomes (non-sterile-site LOI)

- 1) Culture-negative meningitis (CSF pleocytosis (WBC>20, and cultures negative as often empirically started on antibiotics prior to CSF collection)
- 2) Single blood culture positive with coagulase-negative staphylococci
- 3) Abdominal infection (includes necrotizing enterocolitis, spontaneous intestinal perforation, and intra-abdominal collection)
- 4) Pneumonia (clinically determined based on CXR findings and endotracheal tube cultures)
- 5) Clinically diagnosed cellulitis
- 6) Culture-negative sepsis (negative blood cultures with consistent symptomatology as defined above)

Appendix 2

Educational documents/poster for GloveCare arm



Glove-based care for the prevention of late onset sepsis in Neonatal Intensive Care Unit (NICU) patients

Information for Staff

Why are we doing this study?
To find out if healthcare providers wearing gloves in addition to standard hand hygiene for direct patient contact in the NICU reduces the rate of late onset infection when compared to hand hygiene alone.

What is my role in this study as a staff member?

- Depending on the phase of the study, healthcare providers will either:
 - 1) perform hand hygiene as usual or
 - 2) perform hand hygiene as usual and also wear gloves when they are in contact with patients
- Family members, are not required to wear gloves, and can interact and make contact with their baby as usual.


How will I receive updates on the study?

- Rates of late onset infection, and glove and hand hygiene compliance will be posted on the quality board.


Do you have any questions?
 Please contact the Study Coordinator Geoff Travis (travisg@mcmaster.ca) or Investigators: Dr. Sarah Khan (khan259@mcmaster.ca), Dr. Salhab El Helou (elhelos@mcmaster.ca) for more information.

Appendix 3

Monthly study report



GLOVECARE STUDY UPDATE – INFECTIONS AND HAND HYGIENE MONTHLY REPORT



This is a reminder that the **GloveCare Study has started as of JUNE**. We are currently in the **CONTROL arm which means continue with your usual**. So although you may not be GLOVING for all care, we are still collecting data.


INFECTIONS:

| | CSF | BLOOD | URINE | OTHER |
|--------|-----|---------------|-------|------------------------------------------|
| JUNE | 0 | 1 0 CLABSI | 0 | 1 STOOL VIROL |
| JULY | 1 | 1 0 CLABSI | 2 | 2 ETT |
| AUGUST | 0 | 0 | 1 | 4 ETT 1 ESBL SWAB 3 SERRATIA SWABS |

HAND HYGIENE: (TARGET >90%)

| | Before patient/ environmental contact | After patient/ environmental contact |
|--------|---------------------------------------|--------------------------------------|
| June | 87.6% 106/121 observations | 86.9% 172/198 Observations |
| July | 80.6% 112/139 observations | 86.4% 197/228 observations |
| August | 88.6% 31/35 observations | 92.1% 70/76 observations |

Hand Hygiene: 4 Moments



1. To prevent the patient/caree from acquiring infection from healthcare workers.
 2. To protect the patient against harmful organisms, including the patient's own organisms, entering the body.
 3. To prevent the spread of infection from the patient to the healthcare worker.
 4. To prevent the patient/caree from acquiring infection from the healthcare worker.

Reminder of examples of Aseptic procedures:

- Medication administration (IV or PO)
- NG feed
- Suctioning
- Dressing change
- Bloodwork, Central line care

If you have any questions please contact: (Sarah Khan) khan259@mcmaster.ca or (Geoff RC) travisg@mcmaster.ca

Appendix 4

Pictures of isolette and posters



All health care providers are to **perform hand hygiene and wear non-sterile gloves** before any contact with patients in the NICU at this time



All health care providers are to **perform hand hygiene and wear non-sterile gloves** before any contact with patients in the NICU at this time



Appendix 5

Table 7

Table 7 Self-reporting of episodes of non-compliance with gloving was also implemented with a bedside charting tool

| Date | # of times this shift | Reason (check/comment) | | | | |
|----------|-----------------------|------------------------|------|--------|---------|-------|
| | | Acuity | Tape | Forgot | palpate | Other |
| 11/20/17 | 3 | ✓ | ✓ | ✓ | | |

Appendix 6

Table 8

Table 8 Randomization table of study arms and hand hygiene audits

Weekly shifts:
Random Seed: 6321

| | |
|--------|---------------------|
| Period | Treatment group |
| 1 | Usual care |
| 2 | Gloves + usual care |

Weekly shifts:
Random Seed: 6321

| Week | Date (2017–2018) | Shift 1 | Auditor 1 | Shift 2 | Auditor 1 | Shift 3 | Auditor 1 |
|------|------------------|----------|-----------|----------|-----------|----------|-----------|
| 1 | June 5–June 9 | Mon AM | | Mon PM | | Wed PM | |
| 2 | June 12–June 16 | Wed AM | | Fri PM | | Thurs AM | |
| 3 | June 19–June 23 | Mon AM | | Thurs PM | | Thurs AM | |
| 4 | June 26–June 30 | Tues AM | | Fri AM | | Fri PM | |
| 5 | July 3–July 7 | Thurs AM | | Thurs PM | | Wed PM | |
| 6 | July 10–July 14 | Mon PM | | Mon AM | | Fri PM | |
| 7 | July 17–July 21 | Thurs PM | | Thurs AM | | Wed PM | |
| 8 | July 24–July 28 | Wed PM | | Mon PM | | Thurs AM | |
| 9 | July 31–Aug 4 | Wed AM | | Fri PM | | Mon PM | |
| 10 | Aug 7–Aug 11 | Fri PM | | Mon AM | | Tues AM | |
| 11 | Aug 14–Aug 18 | Wed PM | | Fri PM | | Tues PM | |
| 12 | Aug 21–Aug 25 | Fri AM | | Tues AM | | Mon AM | |
| 13 | Aug 28–Sept 1 | Fri PM | | Thurs AM | | Wed PM | |
| 14 | Sept 4–Sept 8 | Tues PM | | Tues AM | | Thurs AM | |
| 15 | Sept 11–Sept 15 | Tues PM | | Wed PM | | Thurs PM | |
| 16 | Sept 18–Sept 22 | Wed AM | | Thurs PM | | Wed PM | |
| 17 | Sept 25–Sept 29 | Thurs PM | | Wed PM | | Mon AM | |
| 18 | Oct 2–Oct 6 | Wed AM | | Fri AM | | Fri PM | |
| 19 | Oct 9–Oct 13 | Tues AM | | Mon PM | | Fri AM | |
| 20 | Oct 16–Oct 20 | Mon PM | | Fri PM | | Tues PM | |
| 21 | Oct 23–Oct 27 | Tues AM | | Wed AM | | Tues PM | |
| 22 | Oct 30–Nov 3 | Tues AM | | Thurs AM | | Mon AM | |
| 23 | Nov 6–Nov 10 | Mon PM | | Wed PM | | Tues AM | |
| 24 | Nov 13–Nov 17 | Thurs PM | | Thurs AM | | Mon PM | |
| 25 | Nov 20–Nov 24 | Wed PM | | Mon PM | | Thurs PM | |
| 26 | Nov 27–Dec 1 | Tues PM | | Wed PM | | Tues AM | |
| 27 | Dec 4–Dec 8 | Fri PM | | Tues AM | | Mon AM | |
| 28 | Dec 11–Dec 15 | Tues PM | | Mon PM | | Thurs AM | |
| 29 | Dec 18–Dec 22 | Wed PM | | Mon PM | | Tues PM | |
| 30 | Dec 25–Dec 29 | Wed PM | | Mon PM | | Mon AM | |
| 31 | Jan 1–Jan 5 | Mon PM | | Thurs AM | | Thurs PM | |
| 32 | Jan 8–Jan 12 | Fri PM | | Thurs AM | | Tues PM | |
| 33 | Jan 15–Jan 19 | Thurs AM | | Fri AM | | Tues AM | |
| 34 | Jan 22–Jan 26 | Thurs PM | | Mon AM | | Fri AM | |
| 35 | Jan 29–Feb 2 | Mon AM | | Fri AM | | Thurs AM | |
| 36 | Feb 5–Feb 9 | Tues AM | | Fri PM | | Thurs AM | |
| 37 | Feb 12–Feb 16 | Tues AM | | Mon AM | | Wed AM | |
| 38 | Feb 19–Feb 23 | Thurs AM | | Wed AM | | Wed PM | |
| 39 | Feb 26–March 2 | Wed PM | | Wed AM | | Fri AM | |
| 40 | March 5–March 9 | Tues PM | | Mon AM | | Fri AM | |

Table 8 (continued)

| | | | | |
|----|-------------------|----------|----------|----------|
| 41 | March 12–March 16 | Thurs AM | Fri AM | Fri PM |
| 42 | March 19–March 23 | Tues AM | Fri AM | Wed PM |
| 43 | March 26–March 30 | Fri AM | Wed PM | Mon PM |
| 44 | April 2–April 6 | Tues PM | Fri AM | Wed AM |
| 45 | April 9–April 13 | Tues AM | Mon AM | Wed AM |
| 46 | April 16–April 20 | Wed AM | Thurs PM | Fri AM |
| 47 | April 23–April 27 | Thurs PM | Tues PM | Mon AM |
| 48 | April 30–May 4 | Mon AM | Thurs PM | Thurs AM |
| 49 | May 7–May 11 | Thurs PM | Mon AM | Wed AM |
| 50 | May 14–May 18 | Fri PM | Tues AM | Thurs PM |
| 51 | May 21–May 25 | Wed AM | Thurs AM | Mon PM |
| 52 | May 28–June 1 | Tues PM | Fri AM | Thurs AM |
| 53 | June 4–June 8 | Fri PM | Thurs AM | Fri AM |
| 54 | June 11–June 15 | Fri AM | Thurs AM | Mon AM |
| 55 | June 18–June 15 | Wed PM | Thurs PM | Tues AM |

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Authors' contributions

SK is the primary author who oversaw the project from commencement to completion. KT assisted with data collection, analysis, and manuscript writing. ZJ assisted with data analysis and manuscript writing. BM assisted with data collection and data validation. SEH assisted with study implementation and education. MS and DK were involved in the study conception and design. JP, LT, DM, and ML were involved in the study design, data analysis and interpretation, and manuscript review. The author(s) read and approved the final manuscript.

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Availability of data and materials

The datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations**Competing interests**

The authors declare that they have no competing interests.

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