Universal Mask Usage for Reduction of Respiratory Viral Infections After Stem Cell Transplant: A Prospective Trial

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Background. Respiratory viral infections (RVIs) are frequent complications of hematopoietic stem cell transplant (HSCT). Surgical masks are a simple and inexpensive intervention that may reduce nosocomial spread.

Methods. In this prospective single-center study, we instituted a universal surgical mask policy requiring all individuals with direct contact with HSCT patients to wear a surgical mask, regardless of symptoms or season. The primary endpoint was the incidence of RVIs in the mask period (2010–2014) compared with the premask period (2003–2009).

Results. RVIs decreased from 10.3% (95/920 patients) in the premask period to 4.4% (40/911) in the mask period (P < .001). Significant decreases occurred after both allogeneic (64/378 [16.9%] to 24/289 [8.3%], P = .001) and autologous (31/542 [5.7%] to 16/622 [2.6%], P = .007) transplants. After adjusting for multiple covariates including season and year in a segmented longitudinal analysis, the decrease in RVIs remained significant, with risk of RVI of 0.4 in patients in the mask group compared with the premask group (0.19–0.85, P = .02). In contrast, no decrease was observed during this same period in an adjacent hematologic malignancy unit, which followed the same infection control practices except for the mask policy. The majority of this decrease was in parainfluenza virus 3 (PIV3) (8.3% to 2.2%, P < .001).

Conclusions. Requiring all individuals with direct patient contact to wear a surgical mask is associated with a reduction in RVIs, particularly PIV3, during the most vulnerable period following HSCT.

Keywords. hematopoietic stem cell transplant; infection; prevention; parainfluenza virus; surgical mask.

Respiratory viral infections (RVIs) are a significant complication of hematopoietic stem cell transplant (HSCT), affecting up to 30% of patients [1–3]. In addition to causing rhinitis, cough, and other symptoms, 25%–40% of cases progress to lower respiratory tract infection [4, 5], with associated mortality as high as 20%–40% [6–8].

Because HSCT recipients are immunocompromised and tightly cohorted, they are vulnerable to nosocomial spread. For example, there have been a number of reports of clusters or outbreaks of parainfluenza virus type 3 (PIV3) within HSCT units [5, 9–12]. In many of these cases, molecular epidemiologic analyses have traced these outbreaks to a single or handful of strains that spread through person-to-person transmission [13–18].

While standard infection control procedures serve an essential role in curtailing RVIs [7, 19], it is hypothesized that they may be insufficient to prevent the nosocomial spread of PIV3 [10]. This is because patients (or caregivers or providers) with PIV3 may shed virus, yet be asymptomatic [10, 12, 14–16], and are therefore missed by standard droplet precautions that focus on symptomatic patients. Similarly, strategies that increase infection control measures during the winter influenza and respiratory syncytial virus (RSV) seasons neglect PIV3, which peaks in the summer [5, 9, 11–15, 17, 20].

In 2009, our HSCT unit experienced a higher-than-average incidence of RVI, prompting an exploration for means to better prevent transmission. We hypothesized that instituting an infection control protocol that requires universal surgical mask usage year-round by all individuals in contact with patients peritransplant would complement existing measures (eg, universal hand washing) and provide greater protection against RVI transmission.

MATERIALS AND METHODS

Infection Control and Mask Protocol

Following approval from the Duke University Health System institutional review board, we conducted a prospective interventional trial of the impact of universal surgical mask usage on RVIs. This policy was added to standard infection control practices as implemented and monitored by Duke Hospital Epidemiology and Infection Control (Figure 1). The universal mask policy required all individuals with direct patient ...
contact—medical and support staff, visitors, caregivers, and patients—to wear surgical masks (3M Standard Earloop Mask 1826) when within 3 feet of an HSCT patient. Similar masks have been shown to reduce aerosol shedding of both coarse (>5 µm) and fine (≤5 µm) virus particles [21]. Patients were required to wear masks when traveling outside of their room. Universal surgical mask usage was instituted in both the HSCT inpatient (16 beds) and outpatient day hospital (40 beds) units and associated waiting rooms. Compliance was reinforced by nurses, who were trained during the designated “washout” period, and monitored periodically by independent observers using the same protocol as for monitoring hand hygiene compliance [22]. Because the focus was on reducing nosocomial transmission, patients or caregivers were not required to wear masks when alone at home or alone in their private rooms.

**Patient Population**

Universal surgical mask usage was instituted 1 December 2009. Allowing 6 weeks for implementation and washout, the mask cohort included all patients transplanted between 12 January 2010 and 11 January 2014. This conservative washout period would be expected to be significantly greater than the up to 7-day incubation period for the respiratory viral pathogens of interest [23]. All patients who received a transplant between 1 December 2003 (the earliest date data were available in the electronic record) and 30 November 2009 were considered the premask cohort. Patients were observed from the start of conditioning (pretransplant preparative chemotherapy and/or radiation) to the completion of peritransplant care and discharge. Conditioning, prophylaxis for graft-vs-host disease (GVHD), discharge criteria, and other clinical protocols were unchanged over the course of the study. There was not a significant change in the number of beds in either the hematology/oncology unit or the bone marrow transplant unit through the course of the study.

**Microbiologic Sampling, Diagnosis, and Definitions**

All patients with respiratory symptoms were tested via nasopharyngeal wash, sputum culture, tracheal aspirate, or bronchoalveolar lavage. Presence of virus was determined by direct fluorescence antigen (DFA) or culture (2003–2009), polymerase chain reaction (PCR) (2011–present), or a combination of DFA, culture, and limited PCR (2009–2011) for influenza A and B, parainfluenza virus (PIV) types 1, 2, and 3, adenovirus, and RSV. Because testing for metapneumovirus, rhinovirus, and coronavirus was not performed until 2011, they were excluded from analysis. Death due to RVI was determined by blinded review of the medical record by 3 physicians.

Data was obtained from medical records, the Duke HSCT database, and the Duke Enterprise Data Unified Content Explorer database.
RESULTS

Patient Characteristics

Nine hundred twenty patients were included in the premask cohort and 911 in the mask cohort (Table 1). Groups were balanced in terms of sex, though the mask cohort tended to be older (mean age, 55 vs 50 years, \( P < .001 \)) and included more patients with multiple myeloma (\( P < .001 \)); as a result, a greater proportion received auto-HSCT (622/911 [68.3%] vs 542/920 [58.9%], \( P < .001 \)). Among allo-HSCT recipients, patients in the mask cohort were less likely to have received mismatched donor transplants (73/911 [25.3%] vs 133/920 [35.2%], \( P = .006 \)), particularly human leukocyte antigen–haploidentical transplants, although they were more likely to have received myeloablative conditioning (172/289 [59.5%] vs 196/378 [51.9%], \( P < .05 \)).

Impact of Universal Mask Usage

The overall incidence of RVI dropped from 95 of 920 (10.3%) in the premask cohort to 40 of 911 (4.4%) in the mask cohort (\( P < .001; \) Table 2). This decrease was primarily in PIV3, which dropped from 76 of 920 (8.3%) to 20 of 911 (2.2%) (\( P < .001 \)). There was also a decrease in RSV (16/920 [1.7%] to 11/911 [1.2%]), although this was not significant. The incidence of influenza A and B, PIV1 and PIV2, and adenoviruses were also too low (<1%) to make meaningful comparisons.

The decrease in RVIs was significant among both allo-HSCT (64/378 [16.9%] to 24/289 [8.3%], \( P = .001 \)) and auto-HSCT patients (31/542 [5.7%] to 16/622 [2.6%], \( P = .007 \)). Similarly,

### Table 1. Baseline Patient Characteristics

| Characteristic | Premask (n = 920) | Mask (n = 911) | \( P \) Value* |
|----------------|-------------------|----------------|----------------|
| Male sex       | 536 (58.3)        | 525 (57.6)     | .78            |
| Age, y, mean (SD) | 50 (12.7)        | 54.7 (12.3)    | <.001          |
| Age, y, median (range) | 52 (19–79)      | 57 (18–81)     |                |
| Disease        |                  |                | <.001          |
| Leukemia       | 237 (25.8)        | 186 (20.4)     |                |
| Lymphoma       | 264 (28.7)        | 209 (22.9)     |                |
| PCD            | 291 (31.6)        | 428 (47)       |                |
| MDS/MPD        | 62 (6.7)          | 51 (5.6)       |                |
| Other          | 66 (7.2)          | 37 (4.1)       |                |
| Previous transplant | 15 (1.6)        | 12 (1.3)       | .58            |
| Type of transplant | <.001            |                |                |
| Autologous HSCT | 542 (58.9)       | 622 (68.3)     |                |
| Allogeneic HSCT | 378 (41.1)       | 289 (31.7)     |                |
| Myeloablative b | 196 (51.9)       | 172 (59.5)     | .05            |
| Alemtuzumab b  | 152 (40.2)       | 99 (34.3)      | .12            |
| Mismatch b     | 133 (35.2)       | 73 (25.3)      | .006           |
| Umbilical cord b | 73 (19.3)       | 51 (17.6)      |                |
| Haploidentical b | 60 (15.9)       | 22 (7.6)       |                |

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: cord, cord blood donor; haploidentical, human leukocyte antigen–haploidentical donor; HSCT, hematopoietic stem cell transplant; MDS, myelodysplastic syndrome; MPD, myeloproliferative disorder; PCD, plasma cell dyscrasia; SD, standard deviation.

* Wilcoxon rank-sum test for continuous variables and \( \chi^2 \) test for categorical variables.

b Presented as percentage of patients who received allogeneic HSCT.
both allo-HSCT and auto-HSCT patients experienced large decreases in PIV3 (allo-HSCT: 49/378 [13.0%] to 12/289 [4.2%], *P* < .001; auto-HSCT: 27/542 [5.0%] to 8/622 [1.3%], *P* < .001). Concurrent with this decrease, the rate of death secondary to RVI dropped in the mask cohort (all patients: 11/920 [1.2%] to 0/911 [0%], *P* = .001; allo-HSCT: 9/378 [2.4%] to 0%, *P* = .006, auto-HSCT: 2/542 [0.4%] to 0%, *P* = .217).

The decision to test for viral pathogens was dependent on patient signs and symptoms and clinician concern for viral infection. It was not surprising, therefore, that concurrent with the decrease in RVIs, fewer viral tests were performed in the mask period. However, despite the increased sensitivity of PCR-based tests in the mask period, the proportion of positive test results was lower: 29% of tests were positive premask (95 positive of 328 tests), compared with 15% (25/162) from 12 January 2010 to 11 January 2013 (*P* = .002; data on total tests performed were not available for the last year, and thus are not included in this calculation). This suggests that testing practices for RVIs was more aggressive in the mask period, and the rate of RVIs was truly lower.

### Table 2. Incidence of Respiratory Viral Infections

| Study Group | Premask (n = 920) | Mask (n = 911) | *P* Value* |
|-------------|------------------|---------------|------------|
| **All Patients (N = 1831)** | | | |
| Any virus (excluding metapneumovirus) | 95 (10.3) | 40 (4.4) | <.001 |
| Influenza A | 5 (0.5) | 4 (0.4) | |
| Influenza B | 1 (0.1) | 1 (0.1) | |
| Parainfluenza (any) | 78 (8.5) | 22 (2.4) | <.001 |
| Parainfluenza 1 | 0 (0) | 1 (0.1) | |
| Parainfluenza 2 | 3 (0.3) | 1 (0.1) | |
| Parainfluenza 3 | 76 (8.3) | 20 (2.2) | <.001 |
| Adenovirus | 0 (0) | 5 (0.5) | |
| Respiratory syncytial virus | 16 (1.7) | 11 (1.2) | .35 |

| Study Group | Premask (n = 542) | Mask (n = 622) | *P* Value |
|-------------|------------------|---------------|-----------|
| **Allo-HSCT Patients (n = 667)** | | | |
| Any virus (excluding metapneumovirus) | 64 (16.9) | 24 (8.3) | .001 |
| Influenza A | 4 (1.1) | 3 (1) | |
| Influenza B | 0 (0) | 0 (0) | |
| Parainfluenza (any) | 51 (13.5) | 14 (4.8) | <.001 |
| Adenovirus | 0 (0) | 3 (1) | |
| Respiratory syncytial virus | 14 (3.7) | 5 (1.7) | |

| Study Group | Premask (n = 542) | Mask (n = 622) | *P* Value |
|-------------|------------------|---------------|-----------|
| **Auto-HSCT Patients (n = 1164)** | | | |
| Any virus (excluding metapneumovirus) | 31 (5.7) | 16 (2.6) | .007 |
| Influenza A | 1 (0.2) | 1 (0.2) | |
| Influenza B | 1 (0.2) | 1 (0.2) | |
| Parainfluenza (any) | 27 (5) | 8 (1.3) | <.001 |
| Adenovirus | 0 (0) | 2 (0.3) | |
| Respiratory syncytial virus | 2 (0.4) | 6 (1) | |

Data are presented as No. (%).

**Abbreviations:** allo-HSCT, allogeneic hematopoietic stem cell transplant; auto-HSCT, autologous hematopoietic stem cell transplant.

*χ² test.

### Time-Series Analysis to Adjust for Seasonal and Yearly Variation and Other Potential Confounders

There were substantial seasonal and yearly variations in the incidence of RVI (Figure 2). For example, PIV tended to peak in the summer, whereas RSV and influenza peaked in the winter. Some years (eg, 2005) had particularly severe outbreaks of PIV whereas other years (eg, 2008) saw few or no cases. To rule out the possibility that seasonal or yearly variations confounded our analysis, we conducted a time-series analysis to adjust for the covariates of season and year, as well as age, location, type of transplant, and, for allo-HSCT, conditioning intensity, T-cell depletion, donor, and GVHD (Table 3). Using this model, mask use was estimated to reduce the risk of RVI by 60% after adjusting for covariates (*P* = .017). Other significant variables were season, conditioning intensity, and GVHD.

We also used this model to evaluate the interaction between season and mask use and found that the impact of the mask intervention was greatest in the summer (*P* = .001; Supplementary Table 1). We found no interaction between location (inpatient vs outpatient) and mask use (Supplementary Table 2), suggesting...
that the impact of mask use was not dependent on location. We also found no interaction between location and type of transplant (allo- vs auto-HSCT) (Supplementary Table 3).

Analyses were also performed looking at PIV3 as the endpoint of interest (Supplementary Table 4): mask use was estimated to reduce the risk of PIV3 by 69% after adjusting for covariates (\(P = .016\)).

Comparisons With the Rest of the Hospital
To evaluate the impact of the addition of universal mask usage to standard infection control procedures, we compared the occurrence of PIV3 in the HSCT population to that of the rest of the hospital (which only used masks as part of standard droplet precautions with symptomatic patients) (Figure 3). In the pre-mask period, PIV3 among HSCT patients tracked closely with the PIV3 in the rest of the hospital. However, after the universal surgical mask policy was instituted, the number of PIV3 infections dropped significantly among HSCT patients, whereas it remained high in the rest of the hospital. Before universal mask usage, HSCT patients accounted for 32% (76/233) of all hospital-wide PIV3 infections; this dropped to just 10.4% (20/192) after implementation (\(P < .001\)).

We also compared the HSCT population to a neighboring hematologic malignancy unit that had identical infection control practices with the exception of universal surgical mask usage (Supplementary Figure 1): RVI and PIV3 in the neighboring unit actually increased over time, whereas they decreased in the HSCT population (data from the neighboring unit were not available prior to 1 July 2006).

Compliance
Compliance with universal surgical mask usage was extremely high (>99% among healthcare providers [414 compliant per 415 observations] and 98% among patients/caregivers [193/197]).

Table 3. Negative Binomial Model Results for the Incidence of Any Viral Infection

| Predictor                                           | IRR (95% CI) | \(P\) Value |
|-----------------------------------------------------|--------------|-------------|
| Age at HSCT, y                                      | 1.000 (.988–1.012) | .97        |
| Season                                              |              |             |
| Spring vs fall                                      | 2.597 (1.286–5.245) | .008       |
| Summer vs fall                                      | 3.137 (1.735–5.674) | <.001      |
| Winter vs fall                                      | 2.186 (1.062–4.502) | .03        |
| Year of HSCT                                        | 1.106 (.505–2.423) | .80        |
| Location: inpatient vs outpatient                   | 1.436 (1.913–2.259) | .12        |
| Type of transplant: allo-HSCT vs auto-HSCT          | 1.112 (.596–2.076) | .74        |
| Conditioning intensity: myeloablative vs not myeloablative | 0.394 (.226–.689) | .001       |
| T-cell depletion: alemtuzumab vs no alemtuzumab     | 0.904 (.479–1.705) | .76        |
| Donor: umbilical cord vs not umbilical cord          | 1.037 (1.599–1.794) | .90        |
| Donor: haploidentical vs not haploidentical          | 1.037 (1.642–1.675) | .88        |
| GVHD vs no GVHD                                     | 1.418 (1.010–1.990) | .04        |
| Mask use: mask vs premask (adjusted)                 | 0.398 (.187–.848) | .02        |
| Mask use: mask vs premask (unadjusted)               | 0.484 (.347–.675) | <.001      |

The adjusted model also controls for the time from the start of the intervention (12 January 2010) and the time from the start of the study (1 December 2003) in days. The unadjusted model includes only mask use. After controlling for potential year-to-year variation, the season, conditioning intensity, presence of GVHD, and mask use had a statistically significant impact on RVI (bolded).

The bolded \(P\) values are for those variables that are significantly associated with incidence of any viral infection.

Abbreviations: allo-HSCT, allogeneic hematopoietic stem cell transplant; auto-HSCT, autologous hematopoietic stem cell transplant; CI, confidence interval; GVHD, graft-vs-host disease; HSCT, hematopoietic stem cell transplant; IRR, incidence rate ratio; RVI, respiratory viral infection.
Compliance with hand hygiene was also consistently high (96% among healthcare providers [5672/5934]; data not available for patients/caregivers).

**DISCUSSION**

Although modern infection control practices have helped decrease viral infections and curtail outbreaks, RVIs remain problematic after HSCT [9, 11, 12]. Standard preventive methods include strict hand hygiene, vaccination, active and early surveillance, and contact and droplet isolation of symptomatic patients [27, 28]. However, strategies that focus on symptoms do not address the prolonged asymptomatic shedding of RVIs in immunocompromised patients, including PIV3 [10, 12, 14–16], which can range from 5 to 121 days [10, 12, 14, 20]. It is therefore not surprising that symptom-based surveillance and isolation policies have been reported with mixed results [11, 12, 16]. In one prolonged outbreak of PIV3 at the Fred Hutchinson Cancer Research Center, droplet isolation of aggressively screened symptomatic patients did not impact the duration or severity of the outbreak [16], as was the case at our institution in 2005. In contrast, more success was seen when universal surgical mask usage was instituted in response to a PIV3 outbreak at the Johns Hopkins Sidney Kimmel Comprehensive Cancer Center [12].

Given its effectiveness in controlling an outbreak, universal surgical mask usage shows promise as an inexpensive and easy-to-implement preventative. In addition to directly stopping transmission of viral particles, universal usage may drive a cultural change in providers and patients, heightening awareness of and attention to the importance of infection control. This intervention may be readily applied to other HSCT programs, and in fact, some institutions already require everyone to wear surgical masks during the peak winter influenza season [12]. However, as PIV3 is most common in the spring and summer months, and nosocomial outbreaks of PIV3 can be prolonged and extend beyond the typical season [11, 17], focus on the winter neglects a significant proportion of RVIs.

By requiring universal surgical mask usage year-round, we were able to significantly reduce RVIs after HSCT. The biggest impact was on PIV3, which made up the majority of RVIs. Consistent with the reported literature [2], we also found that GVHD was associated with more RVIs (GVHD patients receive additional immunosuppression including corticosteroids), and myeloablative conditioning was associated with fewer RVIs (these patients are generally healthier, ie, able to tolerate myeloablative conditioning). Interestingly, our model did not find a significant difference between allo-HSCT and auto-HSCT; however, our model controls for inpatient/outpatient stay, taking into account the length of the interval. Because incidence of RVI after allo-HSCT is 3 times that of auto-HSCT, and the length of stay for allo-HSCT is 3 times that of auto-HSCT, controlling for length of stay minimizes the impact of type of transplant.

A limitation of this study is the before-and-after design. There were significant differences between cohorts, such as the increased prevalence of plasma cell dyscrasias, and consequently auto-HSCT, in the mask cohort. However, universal surgical mask usage had a significant protective effect within both the auto-HSCT and allo-HSCT subgroups. Whereas seasonal and yearly variations in RVIs may also bias results, we

![Figure 3. Parainfluenza virus 3 (PIV3) infections after hematopoietic stem cell transplant (HSCT) vs all other hospitalized patients (hospital). The dotted line represents when universal surgical mask policy was instituted. Prior to the mask policy, PIV3 infections among HSCT patients tracked closely with those in the rest of the hospital; after intervention, the number of PIV3 cases dropped dramatically among HSCT patients but remained elevated in the rest of the hospital (P<.001).](https://academic.oup.com/cid/article-abstract/63/8/999/2389110)
found no parallel decrease in the rest of the hospital. Thus, it seems unlikely that natural variation in the rate of RVIs in the community accounts for the observed decrease. This is supported by our time-series analysis, which found a 60% decrease in the risk of RVIs in the mask period after accounting for the covariates of season and year, in addition to disease, type of transplant, and other variables. Additionally, differences in detection methods in the premask period (predominantly viral culture and DFA) vs the postmask period (PCR) could impact the results. However, as PCR is known to be at least 30% more sensitive at detecting viral pathogens compared with DFA and culture, depending on the pathogen, without sacrificing specificity [29, 30], we would expect a bias toward the null. The true effect size of the mask intervention thus may be underrepresented in the current study.

Our interventional study was designed in direct response to a rise in RVI in 2009, which could render it susceptible to effects seen due to regression to the mean. To mitigate this possibility, we collected data over an extended period of 4 full years following implementation of universal mask usage, rather than examining simply 1 season or 1 year. We considered the possibility of testing bias resulting in reduced vigilance in screening for RVIs during the mask period. However, the lower proportion of positive test results in the mask period suggests that testing is more frequent in the mask period—that is, undertesting would not explain the decrease in RVIs. We also considered the possibility that, over the course of the study period, improved hospital-wide infection control efforts over the 10-year span of the study were responsible for the reduction in RVI rates in HSCT patients. However, a concurrent reduction in RVIs was not observed in either an adjacent non-HSCT hematologic malignancy unit or hospital-wide. Moreover, increasing use of more sensitive and specific PCR-based viral diagnostic testing would be expected to increase the detection of RVI during the universal mask period, as was seen in the adjacent hematologic malignancy unit. In contrast, we observed a decrease in RVIs despite this increased sensitivity, raising the possibility that we are underestimating the protective effect of universal mask usage.

In conclusion, we have shown that universal surgical mask usage, which requires all individuals in inpatient and outpatient HSCT facilities with direct patient contact to wear surgical masks regardless of symptoms or season, is associated with a significant decrease in clinically significant RVI, particularly PIV3. This suggests that universal surgical mask usage could be a potent adjunct to standard infection control practices in bone marrow transplant units.

**Supplementary Data**

Supplementary materials are available at http://cid.oxfordjournals.org. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the author.

**Notes**

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*Author contributions.* M. E. H., N. C. C., G. L., C. C., D. B., and K. M. S. were responsible for study protocol development and implementation. K. C. provided database management expertise. J. A. M. S., A. D. S., and M. E. H. provided data analysis and performed chart reviews. S. T., G. B., and T. H. provided statistical expertise and analysis. A. D. S. and J. A. M. S. drafted the manuscript, and all authors contributed.

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