



# Decreased Incidence of Michigan Emergency Department Visits for Febrile Neutropenia Observed after Public Health Measures for the COVID-19 Pandemic

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## ABSTRACT

**Importance:** Masking and social distancing appear to decrease the febrile neutropenia in susceptible populations, especially among patients with hematologic malignancies.

**Objective:** To determine whether COVID-19 infection mitigation efforts, namely masking and social distancing, results in a reduction in the incidence of febrile neutropenia.

**Design:** This was a retrospective cohort study comparing the incidence of FN in the 13 months prior to (Year 0) and 13 months following (Year 1) the Public Health Executive Orders (PHEO) in Michigan. Data voluntarily submitted by Michigan Emergency Departments (EDs) to the National Syndromic Surveillance Program (NSSP) was queried for all ED visits from April 1st, 2019 to March 31st, 2021.

**Setting:** Population based study.

**Participants:** A population-based sample of patients who reported to a Michigan emergency department and on whom data was captured.

**Intervention(s):** Population based masking and social distancing.

**Main Outcome(s) and Measure(s):** The primary study outcome was the incidence of FN as a proportion of emergency visits in the 13-months before and after COVID-19 mitigations efforts, namely masking and social distancing. We hypothesized that there would be a significant decrease in the incidence of FN in the period following the public health executive orders aimed at reducing the spread of the COVID-19 virus.

**Results:** There was a total of 8,979,221 total ED visits captured during the study period. In Year 0 there were 5,073,081 recorded ED visits and 3,906,140 in Year 1, a decrease of 23%. There was a significant reduction in the proportion of total ED visits with a diagnosis of FN, decreasing 13.3% across periods (0.15% vs. 0.13%,  $p=0.036$ ). In patients with a hematologic malignancy the incidence of FN was significantly lower in the period following PHEO (22% vs. 17%,  $p=0.02$ ).

**Conclusions and Relevance:** Our study found a significant association between social distancing and mask guidelines implemented on a large public scale with decreased rates of FN, particularly in those with a hematologic malignancy. These findings may be useful in the design of clinical trials as well as informing future recommendations for the prevention of FN.

**Keywords:** Febrile neutropenia; Masking; Social distancing; Hematologic malignancy

**Abbreviations:** PHEO: Public Health Executive Orders; ED: Emergency Departments; ICD-10-CM: International Classification of Diseases, Tenth Revision, Clinical Modification; FN: Febrile Neutropenia; CRG: Clinically Relevant Groups; GCSF: Granulocyte Colony Stimulating Factor; NSSP: National Syndromic Surveillance Program

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## INTRODUCTION

Febrile Neutropenia (FN) is defined as neutropenia in the setting of a temperature greater than or equal to 100.4°F and is one of the most common and costly complications associated with cancer treatment [1,2]. Granulocyte Colony Stimulating Factor (GCSF) is the most effective prophylaxis against neutropenia and the subsequent development of FN [3,4]. However, little is known about non-pharmacological prevention strategies for FN in at-risk populations.

Currently, FN prevention strategies include hand hygiene and the avoidance of sick contacts and crowds, however the impact of these efforts is unknown [5]. Furthermore, most patients with FN and culture-proven bacteremia are thought to have acquired it by translocation of gut bacteria [6]. We are unaware of any population-based studies evaluating the impact of widespread public health interventions on the incidence of FN.

The public health crisis due to COVID-19 and its corresponding public health interventions provided a unique opportunity to evaluate the impact of social distancing and masking on the incidence of FN. In March of 2020, the state of Michigan issued an Executive Order that urged residents to remain at home and socially distanced whenever feasible, which was all ended shortly thereafter to include a mask mandate [7]. The aim of our study was to evaluate the association of these mitigation efforts and the incidence of FN in patients presenting to Emergency Departments (EDs) in the state of Michigan.

## METHODOLOGY

This is a retrospective cohort study comparing the incidence of FN in the 13 months prior to (Year 0, March 1, 2019-March 31, 2020) and the 13 months following (Year 1, April 1, 2020-April 31, 2021) the Public Health Executive Orders (PHEO) in Michigan. Approximately 89% of EDs across Michigan voluntarily submit encounter data (patient's chief complaint, associated diagnoses, age, sex, intake temperature, intake percent oxygen saturation, and blood pressure) to the National Syndromic Surveillance Program (NSSP). It was queried for all encounters with a diagnosis of Neutropenia International Classification of Diseases, Tenth Revision, Clinical Modification Diagnosis code 70 (ICD-10-CM D70) from March 1, 2019-April 31, 2021. Febrile neutropenia was defined as an intake temperature greater than or equal to 100.4°F and an ICD-10-CM D70. The incidence of FN in Year 0 was compared to the incidence of FN in Year 1. To account for the impact of the COVID-19

pandemic on total ED visits, the incidence of each International Classification of Diseases (ICD) code was analyzed as a proportion of ED visits for the corresponding year. Associated ICD-10-CM codes were grouped according to Clinically Relevant Groups (CRG) (Supplementary Table 1), modified from the Healthcare Cost and Utilization Project [8]. Analysis of incidence of FN in each CRG was also performed. A visit containing multiple ICD-10-CM diagnostic codes was included in multiple CRGs, if applicable. This study was deemed exempt by the responsible institutional review board.

## Statistical analysis

Descriptive statistics were generated to characterize the study cohorts. Continuous variables are described as the mean with standard deviation or median with range or interquartile range. Categorical variables are described as frequency distributions. Univariable analysis of factors associated with FN was assessed using student's t-test, analysis of variance, and the chi-squared analysis. Multivariable analysis was done using logistic regression. Analyses were conducted using SPSS version 25.0 and p-value less than 0.05 was considered statistically significant.

## RESULTS

From March 1st, 2019 to April 31st, 2021 there were 8,979,221 total ED visits in the state of Michigan that had data submitted to the NSSP with at least one viable ICD-10 code. In Year 0, there were 5,073,081 recorded ED visits and 3,906,140 in Year 1, a decrease of 23%. There were a total of 5,717 encounters with a diagnosis consistent with neutropenia. The proportion of neutropenic patients with a diagnosis of FN presenting to ED did not change significantly before and after PHEO (23% vs. 21%,  $p=0.09$ ) (Table 1). There was, however, a significant reduction in the proportion of total ED visits with a diagnosis of FN, decreasing 13.3% from Year 0 to Year 1 (0.15% vs. 0.13%,  $p=0.036$ ).

In a sub-analysis of all patients with FN, the proportion of patients with FN and associated diagnosis of hematologic malignancy was significantly lower in the period following PHEO as well (22% vs. 17%,  $p=0.02$ , Table 2). In Year 0 there was a 29.3% incidence of FN in neutropenic patients with a CRG of hematologic malignancy, versus a 21.2% incidence in neutropenic patients without a CRG of hematologic malignancy ( $p<0.0001$ , Table 3 and Figure 1). This difference was not observed in Year 1 (23.8% vs. 20.2%,  $p=0.12$ ). Hematologic malignancy was the only CRG diagnosis to have a relatively higher rate of FN in Year 0 compared to Year 1.

**Table 1:** Baseline demographics of neutropenic patients pre- and post-PHEO.

	Year 0 <sup>a</sup> n=3276	Year 1 <sup>b</sup> n=2441	p-value
Sex/Gender			
Male	1572 (48)	1189 (49)	0.59
Female	1704 (52)	1252 (51)	
Age (years)	55.1+23.6	54.7+23.7	0.55

**Note:** Data reported at Mean+SD or n (%) unless otherwise specified Public Health Executive Orders (PHEO) from Governor's Office includes the 13 months prior to Michigan's state-wide PHEO and COVID-19 mitigation efforts; March 1, 2019 to March 31, 2020

<sup>b</sup>Includes the 13 months following Michigan's state-wide PHEO and COVID-19 mitigation efforts; April 1, 2020-April 31, 2021

**Table 2:** Frequency of crg diagnosis among patients with neutropenic and febrile neutropenia in year 0 and year 1.

Diagnoses	Neutropenia		p-value	Febrile neutropenia		p-value
	Year 0 <sup>a</sup>	Year 1 <sup>b</sup>		Year 0 <sup>a</sup>	Year 1 <sup>b</sup>	
	n=3276	n=2441		n=740	n=505	
Common infections	1482 (45)	974 (40)	<0.0001	403 (55)	255 (51)	0.17
Any malignancy	1237 (38)	833 (34)	0.01	276 (37)	182 (36)	0.65
Solid malignancies	722 (22)	511 (21)	0.32	120 (16)	101 (20)	0.09
Hematologic malignancies	564 (17)	357 (15)	0.01	165 (22)	85 (17)	0.02
Benign neoplasms	147 (5)	111 (5)	0.91	43 (6)	17 (3)	0.05
Non-malignant blood dyscrasias	1580 (48)	1213 (50)	0.27	315 (43)	227 (45)	0.41
Endocrine, nutritional, and metabolic disorders	1485 (45)	1119 (46)	0.70	268 (36)	200 (40)	0.23
Skin, musculoskeletal, psychiatric, and nervous system disorders	1224 (37)	870 (36)	0.18	211 (29)	134 (27)	0.44
Disorders of the cardiopulmonary system	1639 (50)	1125 (46)	0.003	324 (44)	210 (42)	0.44
Disorders of the gastrointestinal and genitourinary systems	1332 (41)	952 (39)	0.21	226 (31)	159 (32)	0.72
COVID-19	6 (0)	207 (9)	<0.0001	0 (0)	45 (9)	-

**Note:** Data reported at Mean+SD or n (%) unless otherwise specified

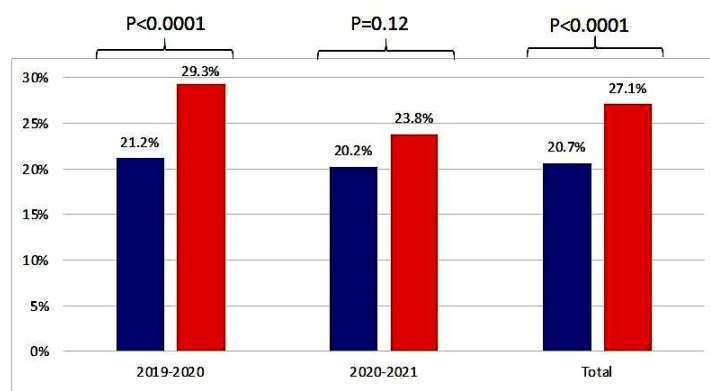
<sup>a</sup>Includes the 13 months prior to Michigan's state-wide PHEO and COVID-19 mitigation efforts; March 1, 2019 to March 31, 2020

<sup>b</sup>Includes the 13 months following Michigan's state-wide PHEO and COVID-19 mitigation efforts; April 1, 2020-April 31, 2021

**Table 3:** Baseline demographics of febrile neutropenic patients vs. patients without febrile neutropenia diagnosis amongst neutropenic patients.

	No diagnosis of febrile neutropenia n=4472	Febrile neutropenia n=1245	p-value
Sex/Gender			
Male	2145 (48)	616 (50)	0.35
Female	2327 (52)	629 (50)	
Age (years)	56.2+22.6	50.3+26.6	<0.0001
SpO2 Percent on Admission	97.1+4.2	96.9+3.2	0.14

**Note:** Data reported at Mean+SD or n (%) unless otherwise specified



**Figure 1:** Incidence of febrile neutropenia in patients with an associated diagnosis of hematologic malignancy compared to those without a diagnosis of hematologic malignancy. Patients with a diagnosis of a hematologic malignancy were significantly more likely to be febrile than those without a diagnosis of hematologic malignancy in Year 0 (21.2% vs. 29.3%,  $p<0.0001$ ). This difference was not seen after implementation of public health guidelines in Year 1 (20.2% vs. 23.8%,  $p=0.12$ ). Note: (■) Any hematologic malignancy; (■) No hematologic malignancy.

## DISCUSSION

The public health response to COVID-19 in the state of Michigan provided a unique opportunity to analyze the impact of social distancing and masking on FN. Masking and social distancing designed to prevent the spread of COVID-19 have resulted in the decline of other non-covid viral illnesses [9,10]. Our study is the first to document an association between this phenomenon and a decline in rates of FN, both overall and in patients with an ICD-10-CM diagnosis consistent with hematologic malignancy.

In the majority of cases, the underlying cause of FN is unknown, and therefore little is known about the efficacy of non-pharmacological efforts to prevent development of FN in neutropenic patients [11]. Our study is the first to report an association between implementation of public health measures to prevent the spread of communicable diseases and a significant reduction in cases of FN associated with hematologic malignancies (22% vs. 17%,  $p=0.02$ ). This is an important finding as patients with hematologic cancers are particularly vulnerable to FN and its associated morbidity and mortality [12].

### Strengths and limitation

This study's strengths include the large number of encounters and associated accurate objective data points (ICD codes and temperature). Additionally, Michigan adopted the stay-at-home orders and mask mandates quickly and broadly, with one of the highest compliance rates of the country during Year 1 (Supplemental Figure 1) [13]. As a result, we were likely able to accurately assess the effect of COVID-19 mitigation efforts on FN.

Our study has several limitations in addition to the inherent vulnerability to unmeasured biases found in retrospective studies: 1) There may be a small number of encounters of FN that are missed in this dataset; 2) Only the intake vital signs were available, and a temperature of 100.4°F was selected as the cutoff for diagnosing FN (rather than 101°F) in an effort to have a more inclusive cohort; 3) Each ED visit was treated as a separate encounter. Therefore, a patient with FN who presented to the ED on multiple occasions would be captured multiple times; 4) It is impossible to account for individual patient hesitancy on presenting to ED [14]; 5) Charts review was not possible, so the effect of active myelosuppressive

therapy could not be assessed; 6) The number and identify of facilities contributing data changes over time, and the use of diagnosis codes could be inconsistent across and within facilities.

## CONCLUSION

Our study found a significant association between the implementation of social distancing and mask guidelines, and a decreased rate of FN in ED patients with neutropenia. This reduction was most pronounced in those with an associated diagnosis of hematologic malignancy. These findings may be useful in the design of clinical trials as well as informing future recommendations for the prevention of febrile neutropenia.

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