Incidence of Serious Infection Events in People With Chronic Neutropenia—Analysis of Real-World Data From Patients in the United States

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Background

- Chronic neutropenia encompasses multiple blood diseases with different etiologies resulting in absolute neutrophil counts (ANCs) <1500 cells/µL for >3 months^{1,2}
- Based on the magnitude of decrease in ANC, neutropenia can be classified as mild (1000 to <1500 cells/µL), moderate (500 to <1000 cells/µL), or severe (<500 cells/µL)^{1,3}
- An important clinical consequence of neutropenia is an increased risk of recurrent and/or severe infections, with the highest risk of infection occurring with ANC <500 cells/µL⁴
- A critical need exists for evidence of incidence and severity of infection events to better understand the necessity for treatments that could reduce or prevent chronic neutropenia in this population
- Despite recent progress in understanding the pathophysiology and treatment of neutropenia, limited data are available for the real-world infection risk in people with chronic neutropenia
- To our knowledge, the association between annual incidence of serious infection events (SIEs) and severity of chronic neutropenia in the US has not been previously reported

Objectives

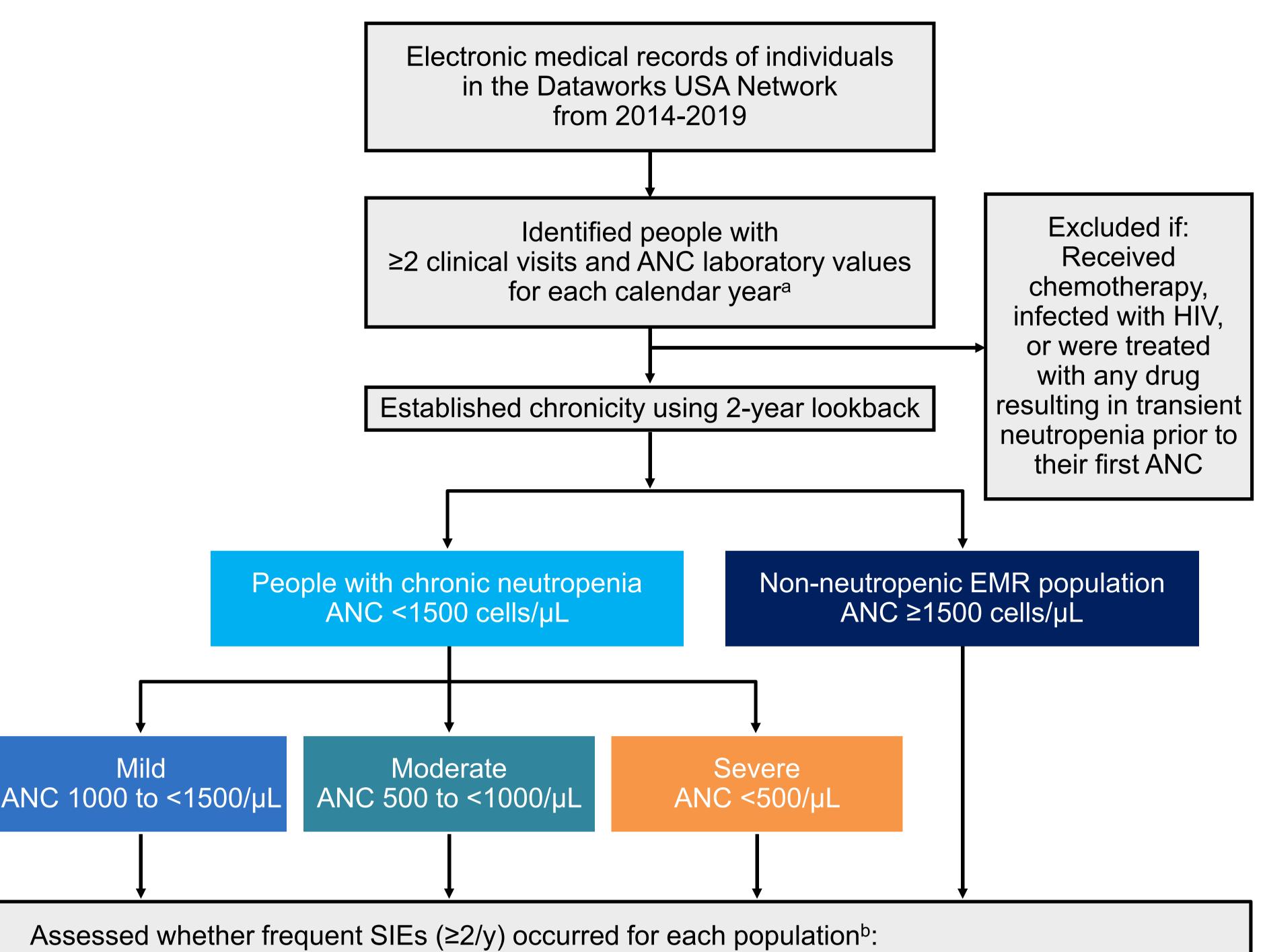
 This study aimed to determine estimated annual incidence of SIE in people with chronic neutropenia with frequent SIEs (≥2/y), defined as events hospitalization or administration of intravenous antibiotics, or resulting in disability or death, in a real-world US population

Methods

- This is a retrospective, cross-sectional cohort study utilizing medical records from the Dataworks USA Network (TriNetX, LLC) electronic medical record (EMR) database for each calendar year from 2014–2019
- The study flow chart and design are shown in Figures 1A and 1B
- Incidence rates were calculated using a denominator of 100,000 person-days at risk, with the numerator representing the number of people with chronic neutropenia who experienced both a laboratory abnormality (ANC <1500 cells/µL) in the year of interest and ≥2 times during a 2-year lookback period, and SIEs

Methods

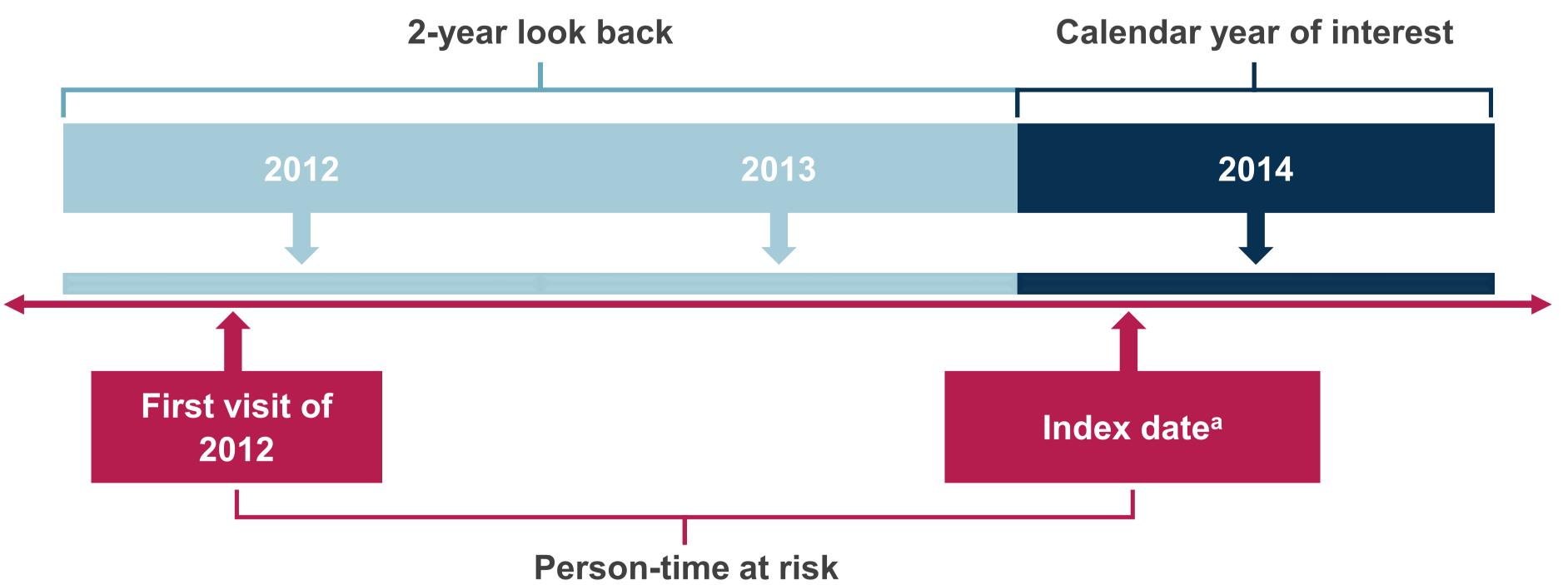
Figure 1A. Study Flow Chart



- 1. To determine annual incidence of SIEs and mortality and compare with non-neutropenic EMR population
- 2. To determine annual incidence of SIEs stratified ANC (<500 cells/µL, 500 to <1000 cells/µL, and 1000 to <1500 cells/µL)

^aThe index date was the date of the second SIE of that calendar year if multiple SIEs occurred. bSIEs were defined as any infection diagnoses identified by an ICD-10 code for infection from a prespecified list that required hospitalization or intravenous antibiotics, or that resulted in disability or death.

Figure 1B. Study Design of the EMR Analysis (Example Year 2014)



alndex date was defined as the date of the 2nd SIE in the year of interest for those who experienced 2 SIEs or the date of the second clinical visit in the year of interest for those who did not experience 2 SIEs.

Limitations

- The study was a retrospective study and used a network of health care organizations
- Patients in the United States may receive treatments and laboratory tests outside of network that may not be captured in the database
- Newly diagnosed patients were likely excluded from this study, since they may not have a history of ANC <1500 in the previous 2 years
- The study focused on people who experienced ≥2 SIEs, rather than the annual incidence of all SIEs
- The study consisted of patients who had ≥2 clinical visits and ANC values, therefore, the number of infections in this group might be overrepresented compared with the normal population
- Analysis likely included people with Duffy-Null Associated Neutrophil Count, who may not have frequent SIEs, despite having an ANC of <1500

Results

Demographic and laboratory characteristics of people included in the analysis between 2014 and 2019^a

Table 1. Demographic Characteristics of People Included in the Analysis^a

	2014 n (%)	2015 n (%)	2016 n (%)	2017 n (%)	2018 n (%)	2019 n (%)			
People in the database ^b	33,556,846	38,127,269	43,568,143	50,741,239	57,211,955	63,145,385			
People included in the analysis ^{b,c}	43,218	80,904	100,330	128,823	145,924	149,144			
Aged									
<12 y	4,837 (11)	9,438 (12)	11,906 (12)	14,220 (11)	15,434 (11)	15,556 (10)			
≥12 y	37,479 (87)	70,034 (87)	86,793 (87)	112,803 (88)	128,576 (88)	131,696 (88)			
Sex at birth ^{e,f}									
Male	16,747 (39)	31,508 (39)	39,988 (40)	51,008 (40)	58,763 (40)	60,696 (41)			
Female	26,471 (61)	49,394 (61)	60,340 (60)	77,805 (60)	87,149 (60)	88,434 (59)			
Racee									
White	34,089 (79)	61,234 (76)	74,728 (75)	92,038 (72)	103,363 (71)	104,811 (70)			
African American	5,665 (13)	11,799 (15)	14,787 (15)	20,542 (16)	23,142 (16)	23,703 (16)			
Otherg	3,464 (8)	7,870 (10)	10,815 (11)	16,234 (13)	19,419 (13)	20,630 (14)			

^aAll percentages were rounded to the nearest whole number. ^bPeople in the database and people included in the analysis are not mutually exclusive for each year; the same individual may have been included in ≥1 calendar year. clincluded people with chronic neutropenia who (1) did not receive chemotherapy nor (2) were treated with specific drugs that increase

the risk of transient neutropenia prior to their first ANC <1500 cells/µL and people who were not neutropenic with ANC ≥1500 cells /µL. dPercentages may not equal to 100 due missing age data in the records. ePercentages may not equal 100 due to rounding. ^fSex unknown for <15 patients for each year. ^gIncluded Asian, other, and unknown.

- For all years analyzed, the majority (87%-88%) of people were aged ≥12 years
- The population evaluated included more females than males in each of the analysis years. Most of the included individuals were of White race (**Table 1**)

Table 2. ANC Distribution of People Included in the Analysis

	2014 n (%)	2015 n (%)	2016 n (%)	2017 n (%)	2018 n (%)	2019 n (%)
ANC cells/μl ^{a,b}						
Severe neutropenia, <500	122 (0.3)	237 (0.3)	288 (0.3)	408 (0.3)	441 (0.3)	479 (0.3)
Moderate neutropenia, 500 to <1000	205 (0.5)	444 (0.5)	622 (0.6)	789 (0.6)	908 (0.6)	946 (0.6)
Mild Neutropenia, 1000 to <1500	762 (1.8)	1,513 (1.9)	1,938 (1.9)	2,464 (1.9)	2,841 (1.9)	2,926 (2.0)
Non-neutropenic, ≥1500	42,129 (97.5)	78,710 (97.3)	97,482 (97.2)	125,162 (97.2)	141,734 (97.1)	144,793 (97.1)

^aAll percentages were rounded to 1 decimal place. ^bPercentages may not equal 100 due to rounding.

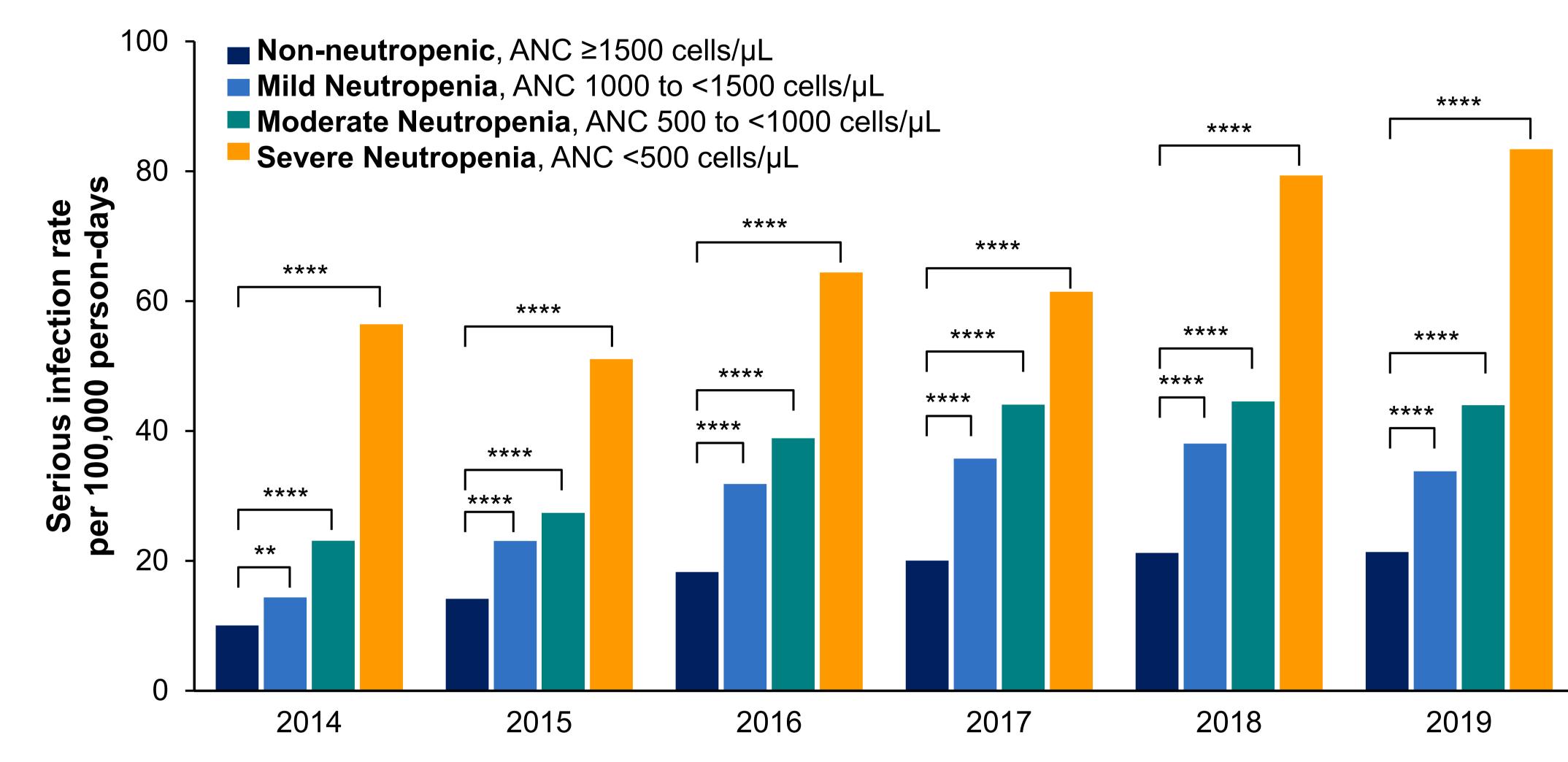
 Of those people who were neutropenic, approximately 10%-11% were severe, 19%-22% were moderate and 67%-70% were mild for all years analyzed

Conclusions

- This is the first large EMR-based analysis of incidence of serious infection events in both adults and children with chronic neutropenia with frequent serious infection events (≥2/y) in the US
- In this real-world analysis, people with chronic neutropenia were found to have a higher estimated annual incidence of serious infection events compared with people in the non-neutropenic EMR population, providing evidence of the burden of serious infection events in people with chronic neutropenia
- Additionally, the incidence of mortality per 100,000 person-days for people with severe chronic neutropenia was significantly greater (consistently ≈7-fold or more; P<.0001 for 2014 to 2019, except 2015; P=.0036 for 2015) vs the non-neutropenic EMR population
- The findings highlight the need for closely monitoring infectious events in people with chronic neutropenia. Preventive strategies should be considered to minimize these events and improve outcomes
- Several key gaps remain, including gaining a more definitive understanding of the types of infections by etiology of chronic neutropenia, long-term outcomes by absolute neutrophil count/etiology of chronic neutropenia, and health care costs associated with serious infection events

Annual incidence rate of SIEs and mortality in people with frequent SIEs (≥2/y) included in the analysis between 2014 and 2019 by severity of neutropenia

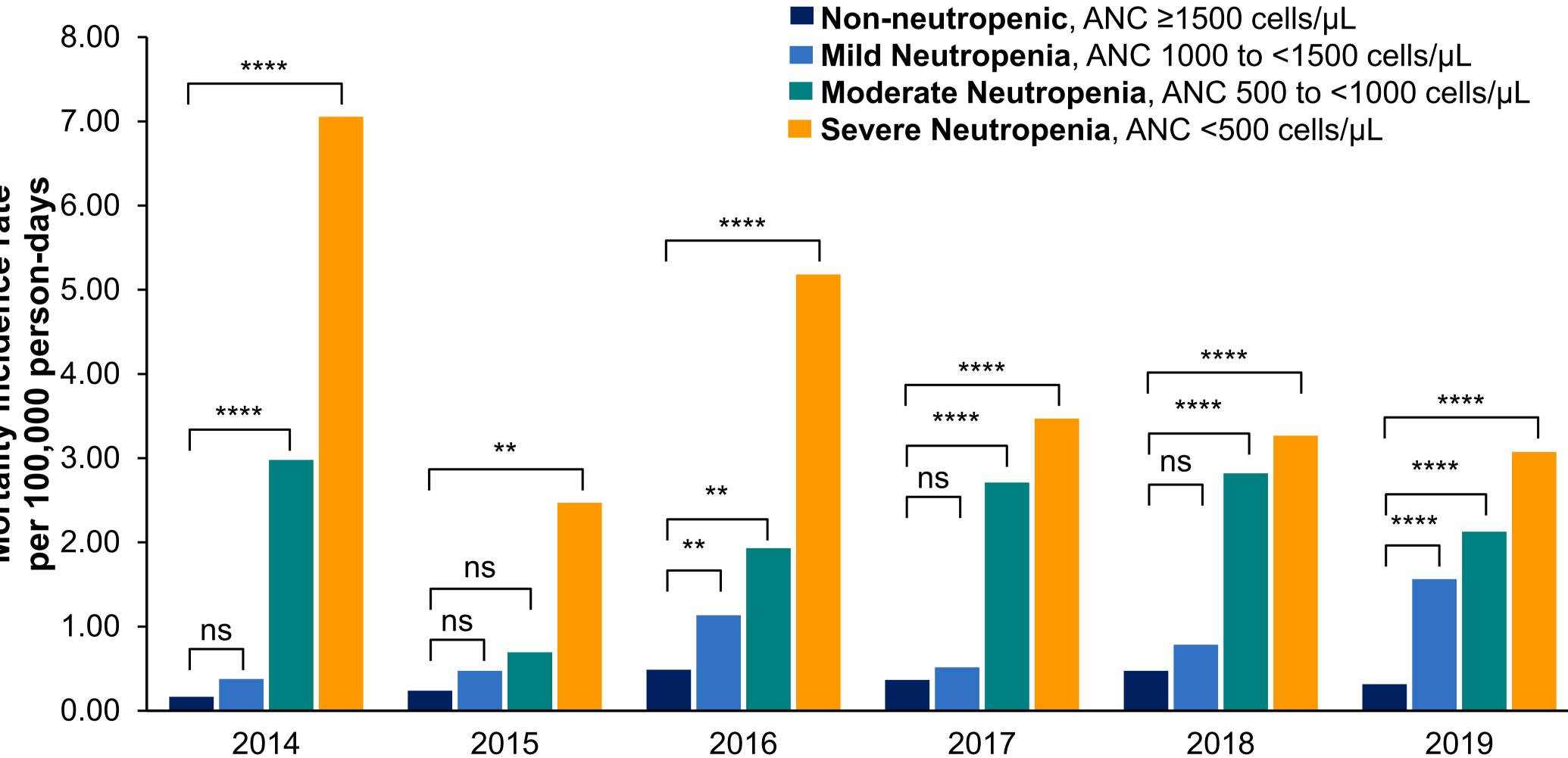
Figure 2. Incidence of SIEs^a



P<.05 are considered statistically significant and set as follows: *—P<.05; **—P<.01; ***—P<.001; ****—P<.0001.

^aRegardless of age, incidence rate of SIEs was 2-fold greater in people with chronic neutropenia vs non-neutropenic EMR population; for the ≥12-year age subgroup, incidence rate of SIEs was >3-fold greater in people with chronic neutropenia and 4- to 6-fold greater in people with severe chronic neutropenia.

Figure 3. Incidence of Mortality^a



P<.05 are considered statistically significant and set as follows: ns—not significant; *—P<.05; **—P<.01; ***—P<.001; *****---P*≤.0001.

^aMortality incidence rate per 100,000 person-days in people with chronic neutropenia (*P* values, chronic neutropenic vs nonneutropenic EMR population) for the years evaluated–2014:1.39 (*P*<.0001), 2015:0.68 (*P*<.0051), 2016:1.62 (*P*<.0001), 2017:1.23 (*P*<.0001), 2018:1.42 (*P*<.0001), 2019:1.81 (*P*<.0001).

1. Newburger PE, Dale DC. Semin Hematol. 2013;50(3):198-206. 2. Donadieu J, et al. Expert Rev Hematol. 2021;14(10):945-960. 3. Fioredda F, et al. Hemasphere. 2023;27;7(5):e897. 4. Anderson CL et al. J Intern Med 2016; 279: 566-575

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Disclosures

KMT is an employee and an equity holder for X4 Pharmaceuticals, Inc, and a former employee and equity holder for Vertex Pharmaceuticals, Inc. DC is a former employee and equity holder for X4 Pharmaceuticals, Inc. JC has served on advisory boards for X4 Pharmaceuticals, Inc. PEN and JW are consultants for X4 Pharmaceuticals, Inc. KW received research funding from X4 Pharmaceuticals, Inc, honoraria from St. Jude, American Society of Hematology, royalties from UpToDate, and has membership on advisory boards for Horizon, Pharming, Sobi, X4 Pharmaceuticals, and AstraZeneca. HJ has no conflicts of interest to report.