The Burden of Opportunistic Infections in Hospitalized Multiple Sclerosis Patients:

A population-based study of 30.3 million hospitalized U.S. patients

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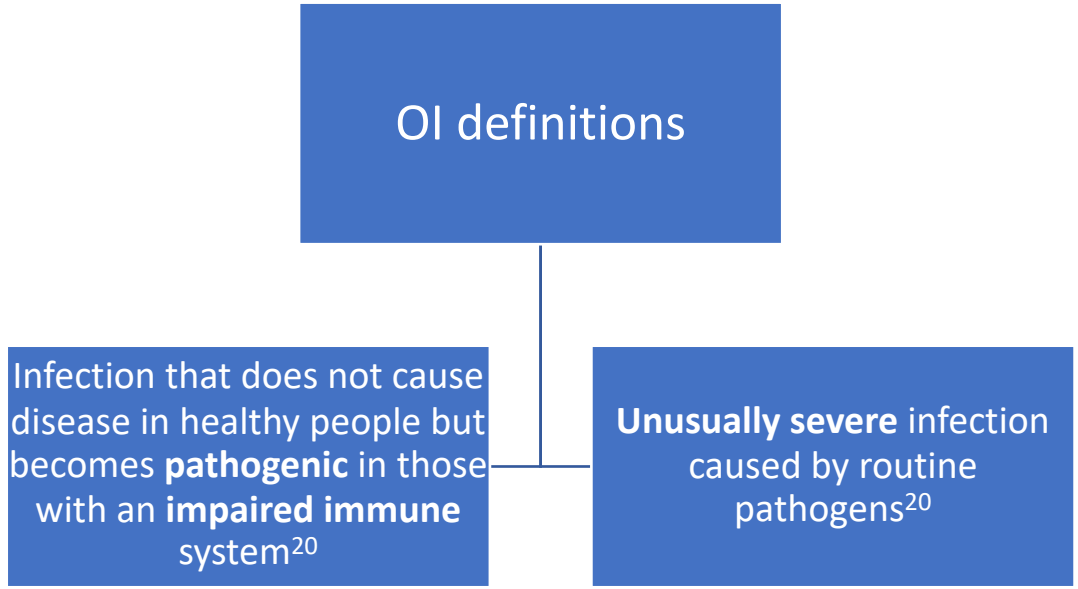
Disclosures

- The presenters have no disclosures to report

Background

- **Opportunistic infections** (OIs) are a serious adverse drug reaction of **disease modifying therapies** (DMTs) used to treat MS[1]
  - Clinical trials: progressive multifocal leukoencephalopathy, herpes, hepatitis B, and disseminated tuberculosis.[2-8]
  - Case reports: cryptococcus, Kaposi sarcoma, toxoplasmosis, pneumocystis pneumonia, nocardiosis, and listeriosis[9-19]
- No existing studies have described or quantified the burden of OIs in MS patients at a population level in the U.S.



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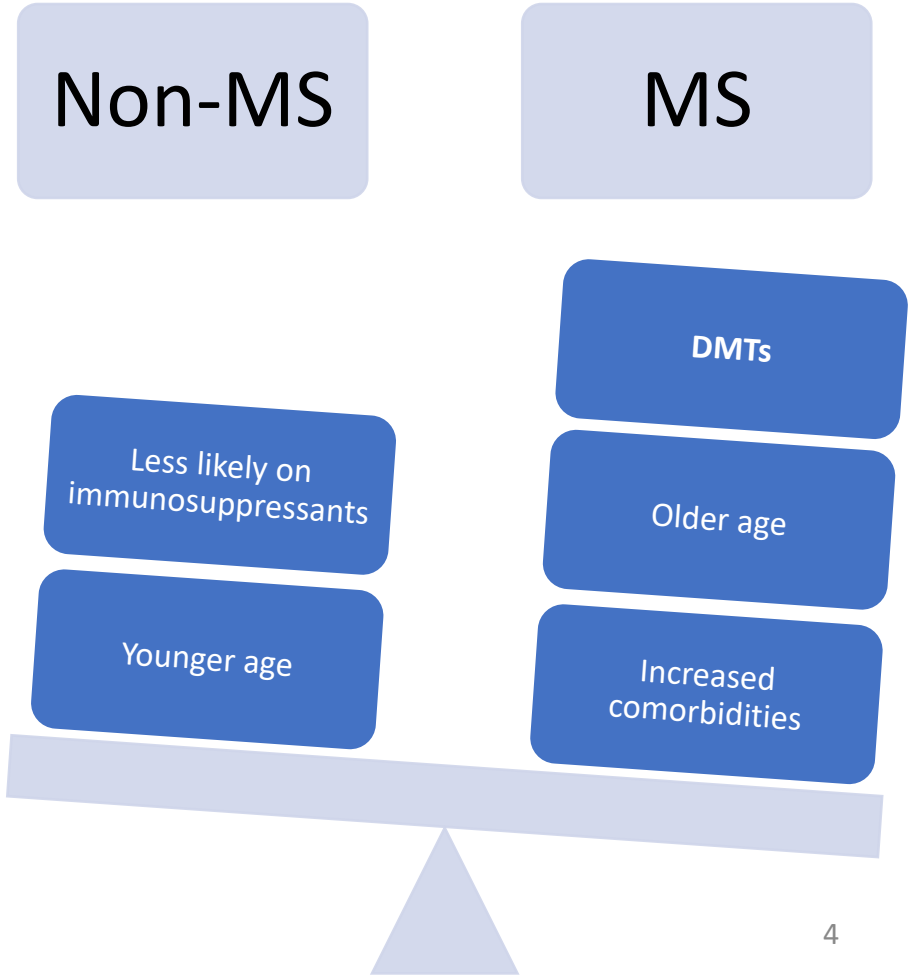
Research question & population

How does the **burden of OIs** in MS patients compare to that in non-MS patients in a nationally representative U.S. sample of hospitalized adults?



Data Source: HCUP-National Inpatient Sample

All-payer

- Includes Medicare Advantage patients—a population often missing from Medicare claims data, but comprises as much as 30% of Medicare beneficiaries

Large sample size (weighted sample >35 million)

- Enables analyses of rare conditions (i.e. OIs) and special patient populations

Provides national estimates

- Approximates a 20-percent stratified sample of discharges from US community hospitals

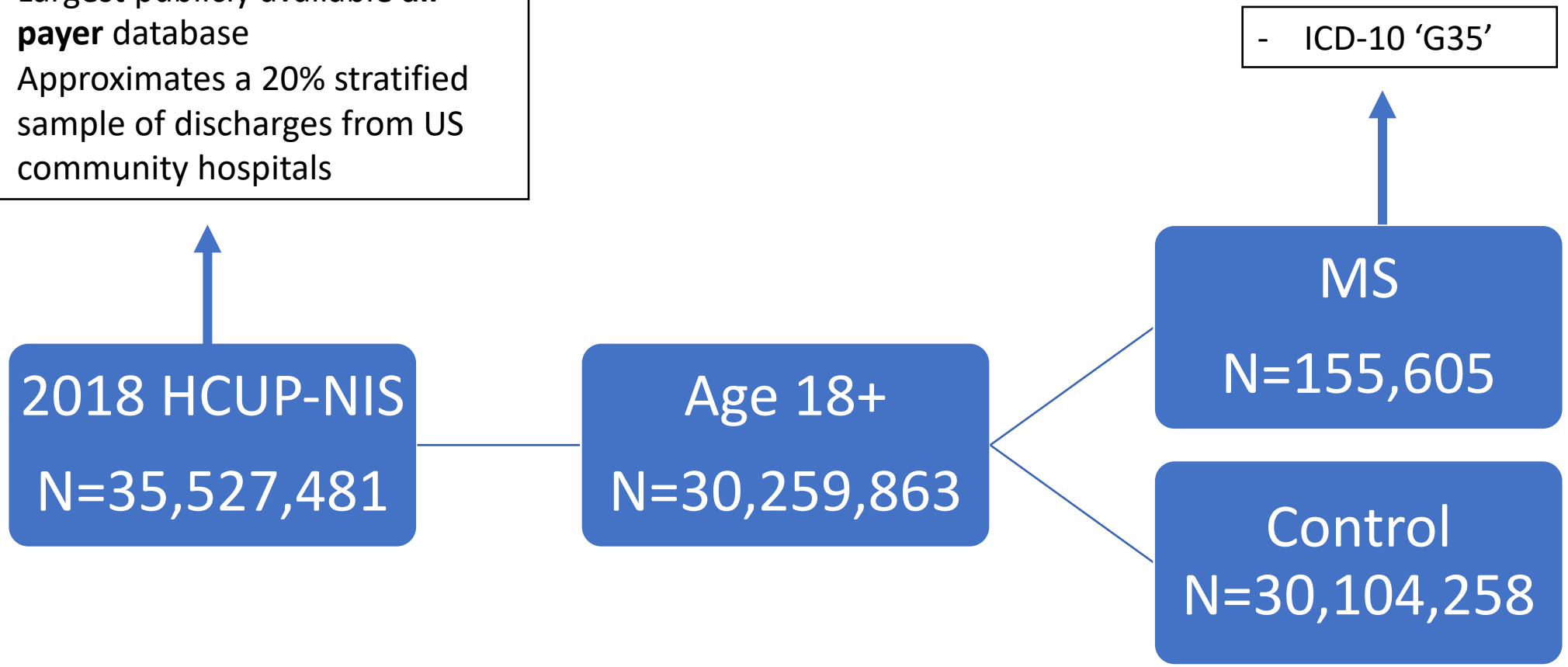
Inpatient records

- Opportunistic infections often require hospitalization

https://www.hcup-us.ahrq.gov/nisoverview.jsp#whats

Study Design – National Inpatient Sample

- Largest publicly available **all-payer** database
- Approximates a 20% stratified sample of discharges from US community hospitals



Outcome – OI Types

- **Bacterial OIs**
  - Invasive group B streptococci
  - invasive Enterobacteriaceae
  - Disseminated tuberculosis
  - Invasive bacterial infection caused by staphylococcus aureus, listeria, pseudomonas aeruginosa, E.coli, klebsiella sp, Haemophilus influenzae, or Serratia
  - Legionella pulmonary infection
  - M. avium disseminated or extrapulmonary
  - Clostridium difficile
- **Fungal OIs**
  - Severe candidiasis
  - Invasive aspergillus
  - Pneumocystis pneumonia
  - Extrapulmonary cryptococcosis
  - Disseminated or extrapulmonary coccidioidomycosis
- **Viral OIs**
  - CMV
  - Epstein-Barr virus
  - Herpesviral encephalitis
  - Systemic varicella
  - Herpes zoster
  - Influenza
  - RSV
  - Human herpesvirus 6 (HHV6) and Human herpesvirus 7 (HHV7)
  - Parvovirus
  - Progressive multifocal leukoencephalopathy
- **Hospital OIs**
  - Nosocomial infection
  - Ventilator associated pneumonia
  - Catheter infection
  - Surgical infection
  - Bloodstream catheter infection
- **Other OIs**
  - Toxoplasma gondii
  - Recurrent pneumonia

Riccardi N et al. *Current Ped Rev.* 2019

Statistical Analysis

Multivariable models (n=6)

- Outcomes: any OI, bacterial OI, viral OI, hospital OI, fungal OI, other OI
- Main predictor: MS
- Covariates: patient and hospital level characteristics

Accounted for in hospital correlations and complex sampling

- Logistic regression (PROC SURVEY LOGISTIC): odds ratios
- Modified Poisson (PROC GENMOD): prevalence ratios

Covariates

Patient level

- Demographics
  - age, sex, race, location
- Primary payer
- Income
- Elective admission
- ED record

Hospital level

- Teaching status
- Hospital control
- Bed size
- Location

Software generated [a,b]

- Pre-existing conditions based on secondary diagnoses[c]
- Tobacco use
- Socioeconomic status

[a]Elixhauser comorbidity software refined for ICD-10 CM: developed by HCUP; identifies pre-existing conditions based on secondary diagnoses (i.e. comorbidities). [b]Clinical classification software: classifies diagnoses into clinically meaningful categories

[c]diabetes, hypertension, depression, obesity, cancer

Baseline characteristics I

- Meaningful demographical differences
  - MS: mostly white females on Medicare
  - Non-MS: greater racial and payer diversity

Variation	MS	Control	P-value
N (weighted)	155,605	30,104,258	
Age (SD)	58.18 (20.4)	56.9 (14.56)	<0.001
Female (%)	72.13	57.29	<0.001
Race (%)			<0.0001
White	74.67	66.89	
Black	16.44	15.09	
Hispanic	2.97	6.48	
Other	5.92	11.54	
Primary payer (%)			<0.0001
Medicare	59.81	47.98	
Medicaid	13.11	18.32	
Private	23.16	26.45	
Other	3.93	7.25	
Median Income Based on Zip Code (%)			<0.0001
1 - 45,999	25.40	29.70	
46,000 - 58,999	26.88	27.04	
59,000 - 78,999	25.69	23.76	
79,000+	22.03	19.50	

Baseline characteristics II

- Meaningful differences in comorbidities between groups

Comorbidities	MS (n=155,605) %	Control (n=30,104,258) %	P-value
Diabetes	21.31	27.32	<0.0001
Hypertension	50.48	53.17	<0.0001
Depression	24.32	12.46	<0.0001
Obesity	17.62	17.33	<0.0001
Tobacco use	17.57	16.77	<0.0001
Leukemia	0.39	0.67	<0.0001
Lymphoma	0.62	0.95	<0.0001
Metastatic Cancer	1.67	3.06	<0.0001
In Situ Cancer	0.02	0.03	<0.0001

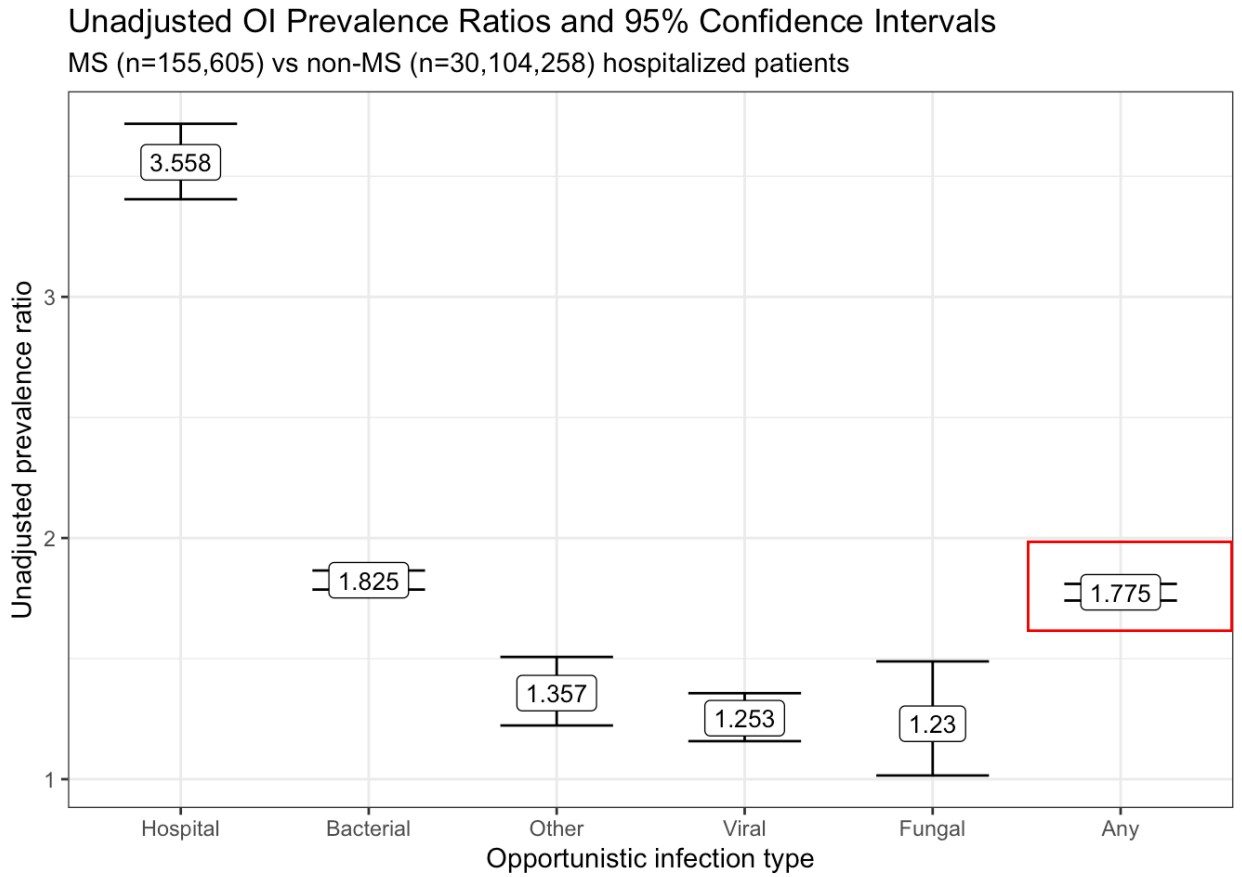
Hospital Characteristics

- MS patients were more likely to have a non-elective admission

Attribute	MS (n=155,605) %	Control (n=30,104,258) %	P-value
Hospital Region (%)			<0.0001
Northeast	21.82	18.56	
Midwest	26.72	22.34	
South	33.41	39.57	
West	18.05	19.54	
Elective Admission (%)	14.92	22.78	<0.0001
Teaching Status (%)			<0.0001
Urban teaching	71.97	70.27	
Urban non-teaching	19.94	20.79	
Rural	8.09	8.94	
Hospital Control (%)			
Voluntary	77.90	73.46	
Proprietary	12.38	15.07	
Public	9.72	11.47	
Hospital Bed size			<0.0001
Small	21.79	21.20	
Medium	29.29	29.18	
Large	48.93	49.62	

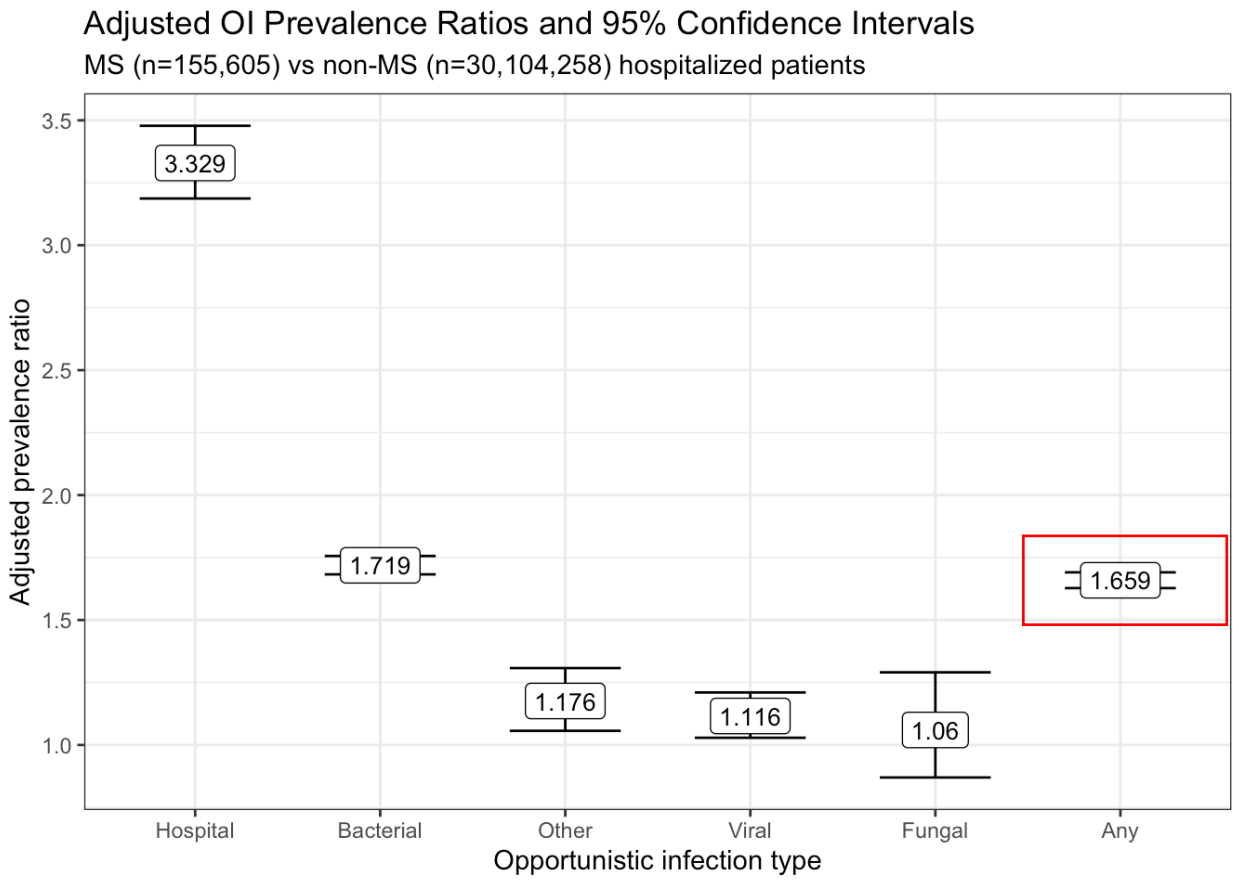
Results: Unadjusted prevalence ratios

Among U.S. hospitalized adults in 2018, the **unadjusted prevalence** of any OI was **77.5% (95% CI: 74.1-81.0%) higher** in MS than non-MS patients.



Results: Adjusted prevalence ratios

Among U.S. hospitalized adults in 2018, the **adjusted prevalence** of any OI was **65.9% (95% CI: 62.8-69.1%) higher** in MS than non-MS patients



Results: Most contributory types of OIs (>1%)

Infection	MS (%)	Control (%)	Prevalence Ratio (95% CI)
Invasive staph, pseudomaonas, E.coli, Klebsiella, Haemophilus, or Serratia	19.76	9.81	2.02 (1.97-2.06)
Invasive enterobacteriaceae	10.51	4.1	2.56 (2.48-2.65)
Catheter infections	6.43	0.6	10.72 (10.26-11.20)
Clostridium difficile	1.51	0.99	1.53 (1.40-1.68)
Nosocomial infections	1.23	0.87	1.42 (1.28-1.56)
Recurrent pneumonia	1.18	0.86	1.37 (1.23-1.51)
Flu	1.10	0.82	1.24 (1.11-1.37)

Invasive gram-negative bacterial infections, respiratory infections, and catheter infections were the **most prevalent** OIs in hospitalized MS patients

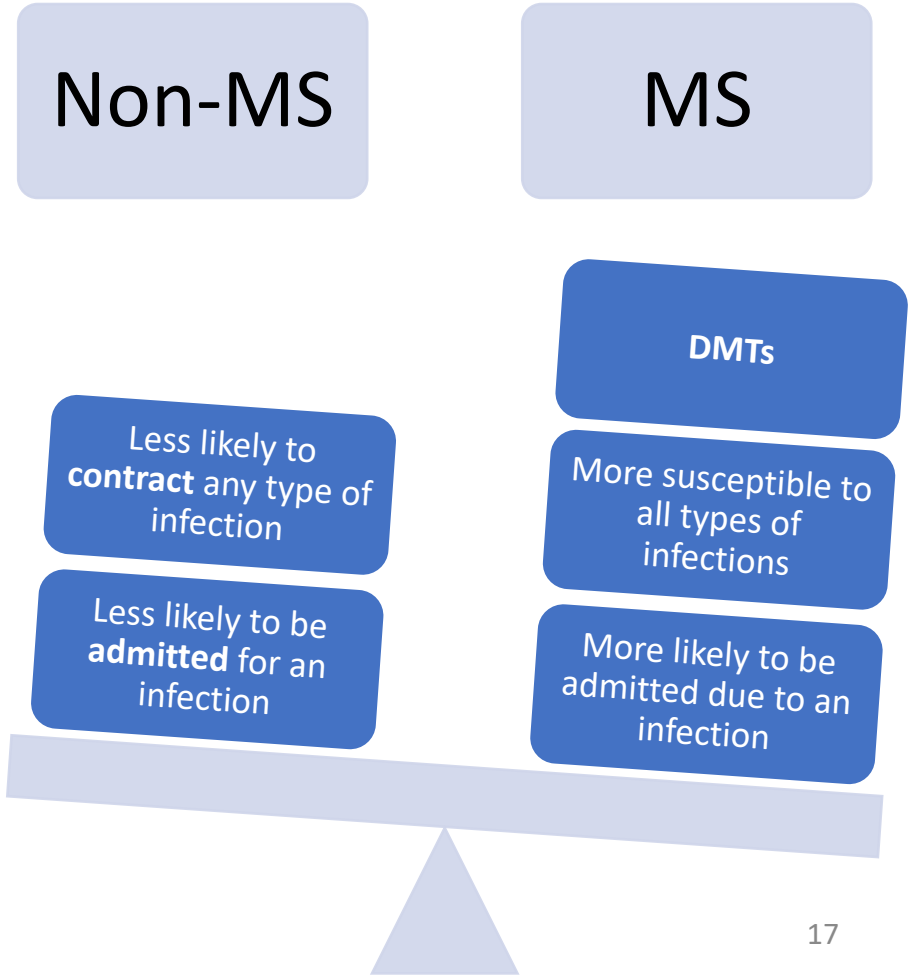
Results: Less common OIs (<1%)

Infection	MS (%)	Control (%)	Prevalence Ratio (95% CI)
Surgical infections	0.54	0.67	0.80 (0.69-0.93)
Zoster	0.35	0.27	1.30 (1.08-1.57)
Severe invasive candidiasis	0.32	0.22	1.43 (1.18-1.74)
Progressive multifocal leukoencephalopathy	0.05	<0.01	15.90 (9.69-26.07)

PML, severe candidiasis, and Zoster infections were the **most prevalent** less common OIs in hospitalized MS patients

Sensitivity Analysis: Research question & population

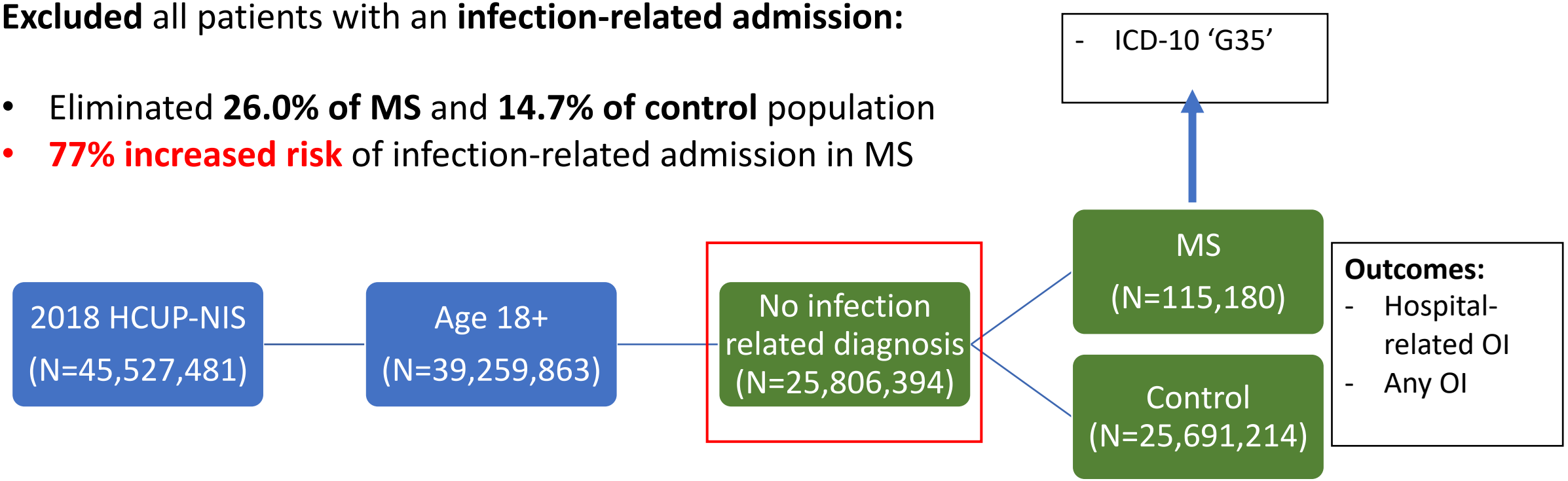
Among a nationally representative US sample of patients **hospitalized for a non-infection related cause**, how does the **burden of hospital acquired OIs** compare in MS to non-MS patients??



Sensitivity Analysis: Population

Excluded all patients with an **infection-related admission:**

- Eliminated **26.0% of MS** and **14.7% of control** population
- **77% increased risk** of infection-related admission in MS



Sensitivity Analysis: Results

Hospital OIs	Estimate	95% CI
Unadjusted prevalence ratio	1.85	1.62-2.10
Adjusted prevalence ratio	1.91	1.67-2.12

Any OIs	Estimate	95% CI
Unadjusted prevalence ratio	1.61	1.55-1.67
Adjusted prevalence ratio	1.53	1.47-1.59

The burden of **OIs remained higher in MS** patients amongst those hospitalized for a non-infection related cause.

Conclusions

- We demonstrated that the **burden of OIs is higher in hospitalized patients with MS compared to those without MS**.
- The finding was largely driven by **hospital acquired and bacterial related OIs** .
- These results were not likely due to the confounding effect of the increased risk of infection-related admissions in MS populations, which was supported in a sensitivity analysis
- Considering the relationship between OIs and adverse outcomes, it is critical to further characterize the relationship in specific MS patient populations (i.e. stratified by race and socioeconomic status).
- Collectively, these findings underscore the importance of infection control in hospitalized MS patients (i.e. not exceeding maximum durations of specific DMTs, Tb testing, immunizations).

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