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Recent anti-infective exposure as a risk factor for first episode of suicidal thoughts and/or behaviors in pediatric patients

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ABSTRACT

Objectives: We conducted a retrospective cohort study of medical records from a large, Maryland, U.S.-based cohort of pediatric primary care patients for potential associations between antibacterial, antifungal and antiviral prescriptions and subsequent suicidal thoughts and/or behaviors.

Methods: Using first suicide-related diagnosis as the outcome and prior prescription of antibacterial, antifungal, and/or antiviral use as the exposure, we employed a series of multivariate Cox proportional hazards models. These models examined the hazard of developing newly recognized suicidal thoughts and/or behaviors, controlling for age, sex, race, insurance, number of encounters during the study period, prior mood disorder diagnosis and number of chronic health conditions. We constructed the same series of models stratified by the groups with and without a prior recorded mental or behavioral health diagnosis (MBHD).

Results: Suicidal thoughts and/or behaviors were associated with the previous prescription of an antibacterial, antifungal and/or antiviral medication (HR 1.31, 95 %-CI 1.05–1.64) as well as the total number of such medications prescribed (HR 1.04, 95 %-CI 1.01–1.08), with the strongest relationship among patients with three or more medications (HR 1.44, 95 %-CI 1.06–1.96). Among individual medications, the strongest association was with antibacterial medication (HR 1.28, 95 %-CI 1.03–1.60). Correlations were strongest among the subgroup of patients with no previous (MBHD).

Interpretation: Infections treated with antimicrobial medications were associated with increased risks of a suicide-related diagnosis among patients who had not had a previous mental or behavioral health diagnosis. This group should be considered for increased levels of vigilance as well as interventions directed at suicide screening and prevention.

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1. Background

Suicide is a critically important public health problem, especially in light of dramatically increasing rates of suicide attempts and suicide deaths among minoritized pediatric populations in the United States (Benton, 2022; Xiao et al., 2021). Suicide-related emergency department visits among pediatric patients saw a 5-fold increase between 2011 and 2020 (Bommersbach et al., 2023). Suicide prevention research has focused extensively on personal, familial, neighborhood and community level factors that may predict suicidal thoughts and/or behaviors, and some important correlates of suicide have been identified, (Fontanella et al., 2015, 2020; Mann and Metts, 2017; Steelesmith et al., 2019) including: a personal history of suicide attempt, drug use, childhood trauma, poor family environment, belonging to a minoritized racial or gender identity group, anxiety, depression and many other demographic, clinical and socioeconomic characteristics (Borowsky et al.,

Abbreviations: MBHD, Mental or behavioral health diagnosis; EMR, Electronic Medical Record; aHR, Adjusted Hazard Ratio; JHCP, Johns Hopkins Community Physicians.

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2001; Perry et al., 2022; Walsh et al., 2023; Prichett et al., 2023).

Less is known about specific biological factors that may be correlated with suicidal thoughts and/or behaviors.

Depression and other psychiatric disorders have been long been linked to inflammation, which is becoming increasingly studied and recorded in relation to suicidal behaviors (Fernandez et al., 2019; Frank et al., 2021). Inflammation has many sources including physical injury, oxidative stress, exposure to food antigens, autoantigens and infectious pathogens (Carmichael et al., 2023). Intriguingly, immune mechanisms responsible for identifying pathogens and clearing infections, such as pathways of the complement system, are also those that are actively engaged during neurodevelopment to cultivate and shape neuronal and glial circuitries (Nimgaonkar et al., 2017). Within the broader immune hypotheses linking infection and psychiatric disease, there is a burgeoning body of neurophysiological research focused on the gut-brain axis, the relationship between the ecosystem of microbiota in the human gastrointestinal tract and neurological health. A leading hypothesis in this field is that a dysregulated microbiome contributes to the development of many common neurological and psychiatric illnesses, including depression, anxiety, bipolar disorder and schizophrenia (Mitrea et al., 2022; Severance et al., 2016a). Systemic anti-infective medications are among the most commonly prescribed medicines in childhood, and while they can be important in fighting infectious diseases, they are also known to substantially alter gut microbiota and microbiome (Mitrea et al., 2022; Slob et al., 2021). Antecedent antibacterial and antifungal medication usage have both been associated with an increased rate of several psychiatric disorders including mania and other mood disorders (Benros et al., 2019; Dickerson et al., 2017; Prichett et al., 2022). However, the association between usage of these antimicrobials and suicide behaviors has not been extensively studied (Yolken et al., 2016; Gjervig et al., 2019; Brundin and Grit, 2016; Lund-et al., 2016). The objective of this study is to examine connections between antimicrobial/anti-infective medication use and subsequent suicidal thoughts and/or behaviors.

2. Methods

This records-based retrospective cohort study was conducted using data from the Johns Hopkins Community Physicians group practice (JHCP), a system that includes 40 locations providing ambulatory general and specialty care throughout the Baltimore-Washington area of the United States. Patient data was extracted from Epic, the electronic medical records system used by JHCP since 2013. The institutional review boards of Johns Hopkins and JHCP approved this study as minimal risk and waived the requirement for informed consent. This study followed STROBE reporting guidelines (Ghaferi et al., 2021).

The study cohort included patients of JHCP pediatric and family practices, ages 8–11 years old as of first encounter in the study time period of January 1, 2013 to December 31, 2021. For this retrospective cohort analysis, patients were excluded if they were 12 years old or older at the time of the first recorded encounter, if there was any suicide-related diagnosis prior to the first recorded antibacterial medication order or at the first encounter (for those without an anti-infective medication order), or if they had a follow up time of less than three years after the first encounter (see Fig. 1). The minimum follow up time was used in order to include only patients likely to come to this particular health system for treatment (i.e. “usual patients”) and the upper age cutoff of 20 was selected in order to best focus on the age group when some of the mental health symptoms most associated with suicidality initially present, ages 12–20 (Pelkonen and Marttunen, 2003). The entry into the population, or study index encounter for each patient, is the time of first JHCP encounter during the study period. Youth with a mental health diagnosis other than a suicide-related diagnosis (see Supplemental Table 1) were retained in the sample if they met all other inclusion criteria.

The outcome of interest was a suicide or intentional self-harm related first diagnosis or problem list recording, which included suicidal ideation, self-harm with suicidal intent, or suicide attempt as indicated by the ICD-9 or ICD-10 encounter diagnosis in the medical record (See Supplemental Table 1 for codes). The primary exposures of interest were defined in five different ways (as indicated by medication order): 1) “ever” exposure to any antibacterial, antifungal and/or antiviral medication, 2) the total number of antibacterial, antifungal and/or antiviral medication orders during the study period, treated both as a continuous variable and a categorical variable (0, 1–2, 3 or more), 3) “ever” exposure to any antibacterial medication, 4) “ever” exposure to any antifungal medication, and 5) “ever” exposure to any antiviral medication. A medication was classified as antibacterial, antifungal, or antiviral based on the therapeutic class listed in the electronic medical record (EMR) medication order.

Demographic data, such as race, ethnicity, age, biological sex and type of insurance was also extracted from each patient’s medical record. Type of insurance was categorized as public, private, or other. In order to control for the potential confounding effects of complex chronic illness, we utilized the Complex Chronic Conditions (CCC) classification system, a classification of ten medical conditions known to last for more than 12 month and/or impact multiple organ systems (Version 2) (Feudtner et al., 2014). We calculated the total number of encounters during the study period as well as an indicator of patients who ever had a diagnosed mood disorder at the index encounter. Any mental or behavioral health diagnosis (MBHD) was defined as a composite of adjustment disorder, anxiety disorder, bipolar disorder, disruptive behavior disorder, mood disorder/depression, impulse control disorder, personality disorder and schizophrenia. Suicide-related diagnosis and MBHD were defined as having an ICD-10 code listed as encounter diagnosis, problem list entry, or referral for outside care and were classified using the Clinical Classifications Software Refined for ICD-10-CM Diagnoses (Supplemental Table 1). (HCUP, 2023)

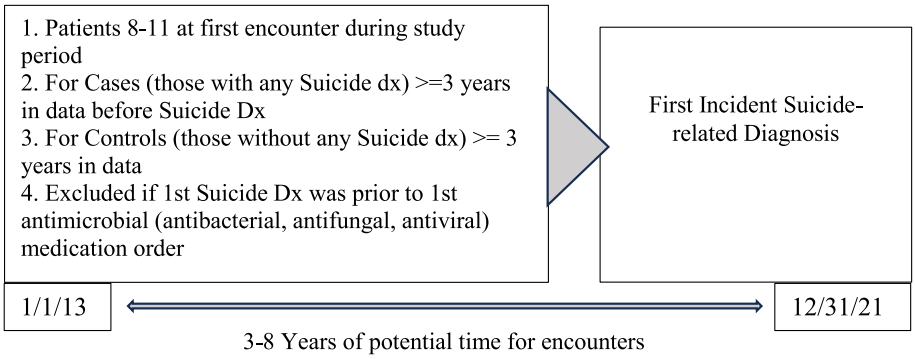

Fig. 1. Conceptual timeline.

Demographic and clinical characteristics of the groups with and without incident suicidal thoughts or behaviors during the study period were compared using Chi-squared tests for categorical variables and Student's t-tests for continuous variables. To examine the risk of suicide-related diagnosis as it related to prescription of antibacterial, antifungal, or antiviral medications, we employed a series of univariate Cox proportional hazards models, followed by multivariate Cox proportional hazards models, controlling for age, sex, race, ethnicity, insurance, number of encounters during the study period, presence of mood disorder diagnosis prior to index encounter and number of CCCs. Confounding variables were chosen based on clinical relevance and significance in univariate analyses.

Additionally, we performed a sub-analysis stratified by presence of previous MBHD in the medical record in order to determine whether effects varied for those with or without a recorded MBHD prior to the index visit. For this sub-analysis, we ran the same series of multivariate Cox proportional hazards models stratified by the groups with and without recorded MBHD at the index encounter (not controlling for baseline mood disorder). All analyses were conducted using Stata software, version 18.0 (College Station, TX).

3. Results

The overarching study cohort consisted of 14,002 patients who met the inclusion criteria. The mean age at first encounter during the study period was 8.9 (SD 0.9) and 6869 (49.1 %) were female. For the measure of race, 7350 (52.5 %) of patients were classified as Non-Hispanic White, 4287 (30.6 %) of patients were non-Hispanic Black, 1119 (8.0 %) were Hispanic and 799 (5.7 %) were non-Hispanic Asian. There was missing data only for race (<1 %) and ethnicity (<2 %) and these observations were grouped into a category labeled "Other/Unknown" category for the analysis. At first recorded encounter, 6868 (49.1 %) of patients had a private primary health insurance and 2899 (20.7 %) of patients had public health insurance. Study cohort patients contributed an average of 5.9 years to the study period (SD 1.8) and an average of 10.4 encounters (SD 7.8).

In terms of recorded MBHDs, 2462 (17.6 %) of patients had a recorded ADHD diagnosis, 2452 (17.5 %) had anxiety disorder, 3112 (22.2 %) had a recorded behavioral disorder, 1012 (7.2 %) had recorded depression and 1861 (13.3 %) had some type of developmental disorder. Less than 1 % of patients had impulse control disorder, personality disorder, or schizophrenia. Over a tenth (10.2 %; n = 1428) of patients had at least one complex chronic condition. A total of 12,581 (89.9 %) did not have a recorded MBHD at the index encounter (Table 1).

Within our cohort, there were 376 (2.7 %) patients with a first suicide-related diagnosis recorded; 6050 (43.2 %) of the patients had any recorded antibacterial, antifungal and/or antiviral prescription during the study period. In terms of the number of prescriptions received, 4543 (32.5 %) received one or two prescriptions of antibacterial, antifungal and/or antiviral medication, and 1416 (10.1 %) received three or more prescriptions. During the study period, 5525 (39.5 %) patients in our cohort received a prescription for an antibacterial medication, 260 (1.9 %) patients in our cohort received a prescription for an antifungal medication and 738 (5.3 %) received a prescription for an antiviral medication (Table 1).

Among the entire analytic cohort of patients (n = 14,002), any antibacterial, antifungal and/or antiviral medication prescription was associated with an adjusted Hazard Ratio (aHR) of 1.31 (95 %-CI = 1.05–1.64) for suicide-related diagnosis. The number of prescriptions of antibacterial, antifungal and/or antiviral medication prescriptions was associated with an aHR of 1.04 (95 %-CI = 1.01–1.08) and three or more antibacterial and/or antifungal prescriptions were associated with an aHR of 1.44 (95 %-CI = 1.06–1.96). Any antibacterial medication was associated with an aHR for suicide-related diagnosis of 1.28 (95 %-CI = 1.03–1.60). There was a possible trend towards an association of antifungal medication and a suicide related diagnosis (HR 1.52, 95 %-CI =

Table 1
Characteristics of the study population by those with and without incident suicide-related diagnosis[a].

	Total	No Suicide-related Diagnosis	Incident suicide-related Diagnosis	P value‡
N	14,002	13,626	376	
Demographics				
Age at 1st JHCP encounter, mean (SD)[b]	8.90 (0.86)	8.90 (0.86)	8.96 (0.89)	0.197
Biological Sex, n (%)				0.004
Female	6869 (49.1)	6650 (48.8)	219 (58.2)	
Male	7123 (50.9)	6966 (51.1)	157 (41.8)	
Nonbinary	8 (0.1)	8 (0.1)	0 (0.0)	
Other/Unknown	2 (0.0)	2 (0.0)	0 (0.0)	
Race/Ethnicity, n (%)				0.625
Black/African American	4287 (30.6)	4165 (30.6)	122 (32.4)	
White	7350 (52.5)	7151 (52.5)	199 (52.9)	
Asian	799 (5.7)	779 (5.7)	20 (5.3)	
Other/Unknown	1566 (11.2)	1531 (11.2)	35 (9.3)	
Ethnicity, n (%)				0.401
Hispanic or Latino	1119 (8.0)	1082 (7.9)	37 (9.8)	
Not Hispanic or Latino	12,481 (89.1)	12,152 (89.2)	329 (87.5)	
Unknown	402 (2.9)	392 (2.9)	10 (2.7)	
Insurance, n (%)				0.003
Public	2899 (20.7)	2821 (20.7)	78 (20.7)	
Private	6868 (49.1)	6712 (49.3)	156 (41.5)	
Other	4137 (29.5)	3998 (29.3)	139 (37.0)	
Time contributed during study period (years), mean (SD)	5.94 (1.79)	5.97 (1.80)	5.04 (1.53)	<0.001
Number of Encounters during Study Period, mean (SD)	10.4 (7.8)	10.2 (7.5)	17.9 (12.3)	<0.001
Mental/Behavioral Health Recorded Diagnoses, n (%)				
ADHD	2462 (17.6 %)	2378 (17.5 %)	84 (22.3 %)	0.014
Anxiety disorders	2452 (17.5 %)	2310 (17.0 %)	142 (37.8 %)	<0.001
Asthma	4225 (30.2 %)	4080 (29.9 %)	145 (38.6 %)	<0.001
Behavioral disorders	3112 (22.2 %)	3006 (22.1 %)	106 (28.2 %)	0.005
Depression	1012 (7.2 %)	916 (6.7 %)	96 (25.5 %)	<0.001
Developmental disorder	1861 (13.3 %)	1792 (13.2 %)	69 (18.4 %)	0.003
Impulse control disorders	53 (0.4 %)	52 (0.4 %)	1 (0.3 %)	0.72
Personality disorders	21 (0.1 %)	19 (0.1 %)	2 (0.5 %)	0.052
Schizophrenia	6 (<1 %)	6 (<1 %)	0 (0.0 %)	0.68
Chronic Condition Classification, n (%)				
Neuromuscular	170 (1.2 %)	159 (1.2 %)	11 (2.9 %)	0.002
Cardiovascular	230 (1.6 %)	220 (1.6 %)	10 (2.7 %)	0.12
Respiratory	38 (0.3 %)	37 (0.3 %)	1 (0.3 %)	0.98
Renal	94 (0.7 %)	87 (0.6 %)	7 (1.9 %)	0.004
Gastrointestinal	135 (1.0 %)	127 (0.9 %)	8 (2.1 %)	0.019

(*continued on next page*)

Table 1 (*continued*)

	Total	No Suicide-related Diagnosis	Incident suicide-related Diagnosis	P value‡
Hematological/Immune System	159 (1.1 %)	136 (1.0 %)	23 (6.1 %)	<0.001
Metabolic	458 (3.3 %)	437 (3.2 %)	21 (5.6 %)	0.011
Congenital/Genetic	355 (2.5 %)	343 (2.5 %)	12 (3.2 %)	0.41
Malignancy	65 (0.5 %)	49 (0.4 %)	16 (4.3 %)	<0.001
Neonatal condition	10 (0.1 %)	9 (0.1 %)	1 (0.3 %)	0.15
Technology Dependent	92 (0.7 %)	86 (0.6 %)	6 (1.6 %)	0.022
Transplant	3 (<1 %)	0 (0.0 %)	3 (0.8 %)	<0.001
Any Presence of CCC	1428 (10.2 %)	1359 (10.0 %)	69 (18.4 %)	<0.001
Number of CCC, mean (SD)	0.13 (0.44)	0.12 (0.43)	0.32 (0.85)	<0.001
Prescription Exposures, n (%)				
Any Antibacterial, Antifungal or Antiviral	6050 (43.2 %)	5817 (42.7 %)	233 (62.0 %)	<0.001
Total number of Antibacterial, Antifungal or Antiviral, mean (SD)	0.9 (1.6)	0.9 (1.5)	1.9 (3.4)	<0.001
Number of Antibacterial, Antifungal or Antiviral				<0.001
0	8043 (57.4 %)	7895 (57.9 %)	148 (39.4 %)	
1-2	4543 (32.5 %)	4404 (32.3 %)	139 (37.0 %)	
3+	1416 (10.1 %)	1327 (9.7 %)	89 (23.7 %)	
Any Antibacterial	5525 (39.5)	5307 (38.9)	218 (58.0)	<0.001
Any Antifungal	260 (1.9)	243 (1.8)	17 (4.5)	<0.001
Any Antiviral	738 (5.3)	706 (5.2)	32 (8.5)	0.004

‡p value is from chi-squared test for categorical variables and *t*-test for continuous variables.

[a] Inclusion criteria: Age 8–11 at first encounter in our data, (Cases) ≥ 3 years in data before Suicide Dx, (Controls), ≥ 3 years in data.

[b] Refers to first encounter during the study period.

0.92–2.48). There was no significant relationship between antiviral medication and subsequent suicide-related diagnosis (Table 2; Fig. 2).

3.1. Subgroup analyses

In the multivariate adjusted Cox proportional hazards analysis with suicide-related diagnosis as the outcome, among those with a co-occurring mental health diagnosis at the index visit (n = 1421), there was a significant relationship between suicide-risk related diagnosis and the total number of antimicrobial medications (aHR of 1.24, 95 %-CI = 1.09–1.39) and a borderline association with any antibacterial medication (aHR 1.27, 95 %-CI = 1.00–1.60). Among the subgroup with no recorded co-occurring MBHD at index visit (n = 12,581), previous prescription of an antibacterial, antifungal and/or antiviral medication was associated with an aHR of 1.34 (95 %-CI 1.05–1.69) and the total number of antibacterial, antifungal and/or antiviral medications prescribed was associated with an aHR of 1.04 (95 %-CI 1.00–1.08) and a strong relationship found was among patients with three or more antibacterial, antifungal and/or antiviral medications prescribed, with an aHR of 1.52 (95 %-CI 1.10–2.11). Antibacterial medication was associated with an aHR of 1.27 (95 %-CI 1.00–1.60). Antifungal medication was associated with a suicide related diagnosis with an aHR of 1.67 (95 %-CI 1.00–2.78). There was not a significant relationship between antiviral medication and subsequent suicide-related diagnosis in this subgroup (Table 2; Fig. 2).

4. Discussion

It is extremely worrisome that suicide in U.S. children not only represents a leading cause of death for this age group but also that rates of suicidal thoughts and/or behaviors are on the rise (Bommersbach et al., 2023; Bridge et al., 2023). With the recent and widespread availability of EMR data in the U.S., we are now able to investigate novel associations in a relatively unexplored and diverse population of children and adolescents living in an urban/suburban region in the United States. In this study, we found that the combination of antibacterial, antifungal and antiviral agents was associated with increased risks of a new-onset suicide-related diagnosis among children, adolescents and young adults living in the U.S.

These findings differ from a study of anti-infective agents including antibiotics, antivirals, antimycotics and antiparasitics in a young cohort from the Danish Health registries. In this large study of Danish medical records, there were no significant associations between anti-infective agents and an increased risk of suicide outcome (Gjervig et al., 2019). These discordant findings require further examination, but they may be a typical reflection of study design heterogeneities or basic differences in geographic, demographic, social and cultural factors. For example, suicide outcomes were defined differently (U.S.: suicide thoughts and/or behaviors vs Denmark: death by suicide). The age ranges of the two cohorts also appear to be quite different (U.S.: 8–20 years vs Denmark: all ages) (Gjervig et al., 2019). The Danish cohort also represents a relatively homogenous White population, whereas our U.S. cohort included a large subgroup of Black patients and somewhat smaller subgroups of Hispanic and Asian pediatric patients. While this U.S. sample is not nationally representative, and thus cannot claim to be generalizable to the entire U.S., it is potentially more generalizable than previous work including homogeneous populations, at least to urban/-suburban regions of the U.S.

Physiological biomarkers that identify individuals at risk for depression and suicide are desperately needed. Immune system dysregulation, infections and imbalances in the gut-microbiome homeostasis all produce a low-level of inflammation that is being increasingly linked to suicidal thoughts and/or behaviors (Brundin and Grit, 2016). These findings support previous work indicating a potential connection between antibacterial use and neuropsychiatric disorders, specifically disorders manifesting as suicidal thoughts and/or behaviors which may be related to disturbances to the microbiome and alterations in the gut-brain axis (Severance et al., 2016a; Slob et al., 2021; Köhler et al., 2017). While understanding the role of the microbiome and its dysbiosis in suicide is our long-term objective, it is not possible in the current manuscript to rule out the effect of active infections on immune and inflammatory pathways. The basic nature of primary care EHR data only allowed identification of a small subset of patients who had a record of antibiotic receipt and lab-confirmed infection, thus making it impossible to tease out role of infection vs antibiotics and even vs the gut microbiome.

While EMR data may be an imperfect data source for time-to-event studies, it is important to develop methodologies for best practices in using such data for research. Ascertainment bias is generally considered a limitation for studies using EMR data, however the growing use of HIE to ensure sharing of patient information, including suicide-related diagnoses, has allowed for improvement in capturing and communicating medical problems such as suicidality from the emergency room to primary care settings. (U.S. Government) Suicidal thoughts and/or behaviors may also be diagnosed via in-office screening in the course of a well-child visit, also improving the odds of underlying suicide risk being recognized, and thus entering a patient's EMR. It should be noted that we chose to cast a "wide net" in terms of suicide-related diagnosis classification by using the complete Clinical Classification Software set

Table 2
Cox Proportional Hazards Model Univariate and Multivariate Regression Results, Incident Suicide-related Diagnosis as modeled "Event"[a].

Exposure	HR	[95 % conf. interval]		P > z	aHR	[95 % conf. interval]		P > z
	Unadjusted				Adjusted			
All Patients (n = 14,002)								
Any Antibacterial, Antifungal or Antiviral	1.85	1.50	2.28	<0.001	1.31	1.05	1.64	0.017
Total number of Antibacterial, Antifungal or Antiviral, mean (SD)	1.12	1.10	1.15	<0.001	1.04	1.01	1.08	0.013
Number of Antibacterial, Antifungal or Antiviral (category)								
0	Reference				Reference			
1-2	1.51	1.20	1.91	<0.001	1.24	0.98	1.58	0.070
3 or more	2.60	2.00	3.39	<0.001	1.44	1.06	1.96	0.019
Any Antibacterial	1.81	1.47	2.22	<0.001	1.28	1.03	1.60	0.029
Any Antifungal	2.08	1.28	3.39	0.003	1.52	0.92	2.48	0.099
Any Antiviral	1.62	1.13	2.33	0.009	1.10	0.76	1.61	0.612
Subgroup with no previous MBHD (n = 12,581)[b]								
Any Antibacterial, Antifungal or Antiviral	1.80	1.44	2.24	<0.001	1.34	1.05	1.69	0.017
Total number of Antibacterial, Antifungal or Antiviral, mean (SD)	1.11	1.09	1.14	<0.001	1.04	1.00	1.08	0.027
Number of Antibacterial, Antifungal or Antiviral (category)								
0	Reference				Reference			
1-2	1.53	1.19	1.95	0.001	1.31	1.02	1.68	0.036
3 or more	2.57	1.94	3.40	0.002	1.52	1.10	2.11	0.011
Any Antibacterial	1.72	1.38	2.14	<0.001	1.27	1.00	1.60	0.047
Any Antifungal	2.26	1.37	3.74	0.001	1.67	1.00	2.78	0.050
Any Antiviral	1.43	0.95	2.15	0.087	1.03	0.68	1.57	0.890
Subgroup with previous MBHD (n = 1421)[b]								
Any Antibacterial, Antifungal or Antiviral	2.30	1.23	4.29	0.009	1.24	0.62	2.48	0.539
Total number of Antibacterial, Antifungal or Antiviral, mean (SD)	1.36	1.22	1.51	<0.001	1.24	1.09	1.39	0.001
Number of Antibacterial, Antifungal or Antiviral (category)								
0	Reference				Reference			
1-2	1.40	0.70	2.77	0.340	0.75	0.32	1.76	0.503
3 or more	2.84	1.34	6.03	0.006	0.71	0.28	1.77	0.460
Any Antibacterial	2.69	1.44	5.02	0.002	1.27	1.00	1.60	0.047
Any Antifungal	0.94	0.13	6.81	0.948	1.67	1.00	2.78	0.050
Any Antiviral	3.13	1.40	7.03	0.006	1.03	0.68	1.57	0.890

[a] Adjusted for age, sex, race, insurance, number of chronic conditions, previous mood disorder diagnosis and number of encounters during the study period.
[b] Adjusted for age, sex, race, insurance, number of chronic conditions and number of encounters during the study period.

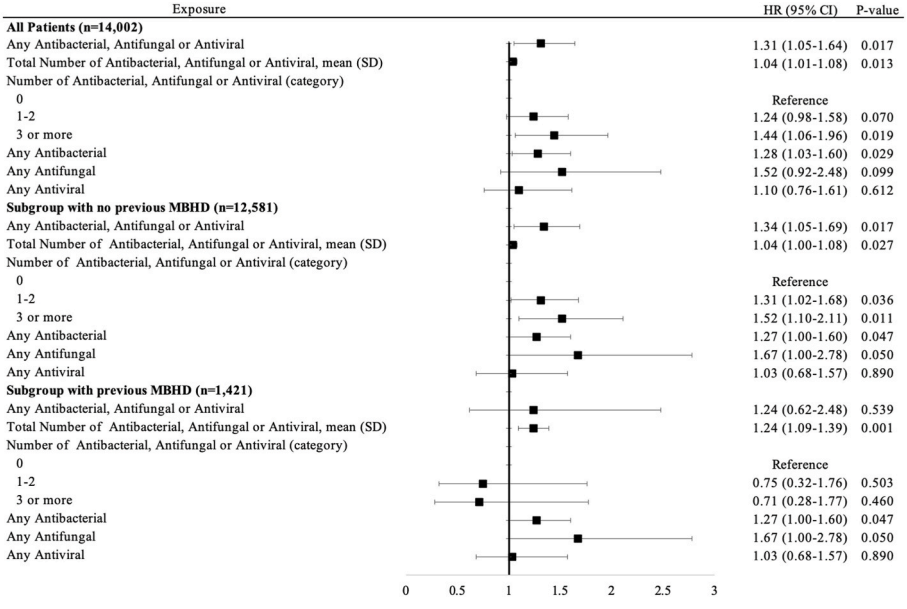

Fig. 2. Forest Plot of Adjusted Hazard Ratios* and 95 % Confidence Intervals. * Adjusted for age, sex, race, insurance, number of chronic conditions, previous mood disorder diagnosis (non-stratified model only) and number of encounters during the study period.

of suicide-related diagnosis codes (including suicidal ideation, suicide attempt and/or intentional self-harm with suicidal intent) to ensure that we do not miss a patient with a recorded suicide-related diagnosis (Bommersbach et al., 2023; HCUP, 2023).

The exposure of interest for this work is the prescription of antibacterial, antifungal and/or antiviral medication. That antiviral medication was not significantly associated with suicide-related diagnosis in any analysis would argue against ascertainment bias as the reason for our findings. That said, we are limited by the nature of outpatient EMR data, in that we are unable to know whether or not a

prescription is filled or whether a medication was taken adherently. We also do not necessarily know if a patient received a prescription medication through an encounter outside of our health system, though we attempted to mitigate this possibility by limiting our inclusion criteria to patients with at least three years of follow up time during the study period. Further research is needed to understand the potential mechanisms for the observed relationships. Given the primary exposures of "any" antibacterial, antifungal or antiviral medication before a subsequently recorded suicide-related diagnosis, we did not have adequate data quality to isolate the underlying infection or infections that were treated by a medication. It is not possible, at this stage, to identify whether the infection or treatment is the true correlate with suicidality. The finding that antifungal medication could be correlated with suicidality is of great interest since fungal infections or the use of antifungal agents have not been previously linked with suicide behaviors among pediatric patients. However, this finding is consistent with previous studies linking exposure to fungal agents such as *Candida albicans* to increased risk of neuropsychiatric disorders such as ADHD, autism spectrum disorder, bipolar disorder and schizophrenia (Hughes and Ashwood, 2018; Severance et al., 2016b; Wang et al., 2023). Another limitation of our study is that we were not able to explore possible mechanisms linking antibacterial or antifungal medication prescription to subsequent suicide behaviors. Mechanisms which have been postulated include antimicrobial alterations in the microbiome as well as the effect of the underlying disorders for which the medications were prescribed (Dickerson et al., 2017; Severance et al., 2016b). Future studies should address these and other possible mechanisms in order to identify pathways which might be amenable to alterations in antimicrobial prescribing practices as well as other possible interventions.

Given the alarming rates of youth suicide, there has been increasing attention on suicide screening and risk assessment. The Joint Commission has mandated screening using a validated tool for suicide assessment in those with a preceding MBHD, and further risk assessment for those that screen positive (The Joint Commission, 2019). Our findings suggest that an understanding of previous antibacterial and antifungal treatment history may aid clinicians in assessing a patient's risk, consistent with previous research on the impact of the microbiome on suicidality. Furthermore, in stratified analysis we found our results were driven by the subgroup patients without a previous MBHD at the index encounter. These findings support previous research suggesting selective screening may be insufficient in identifying patients at risk for suicide, and to consider mandating universal rather than selective suicide screening in youth (DeVylder et al., 2019; Large, 2018).

Data sharing statement

While the dataset used in the work was fully-deidentified by the provisioner of Epic data at Johns Hopkins Medical Institutions, this dataset will unfortunately not be offered as publicly available. This is for two primary reasons: 1) the sensitive nature of this data as pediatric data including measures of mental health; and 2) there is very granular specificity of some data elements, including small numbers within categories, which may make some patients re-identifiable, which would be cause for loss of privacy per HIPAA regulations.

CRediT authorship contribution statement

Laura M. Prichett: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing. **Emily G. Severance:** Conceptualization, Formal analysis, Investigation, Methodology, Resources, Writing – original draft, Writing – review & editing. **Robert H. Yolken:** Conceptualization, Methodology, Project administration, Resources, Writing – original draft, Writing – review & editing. **Destini Carmichael:** Conceptualization, Project administration, Writing – original draft, Writing – review & editing. **Yongyi Lu:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Yong Zeng:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Validation, Visualization. **Andrea S. Young:** Conceptualization, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Tina Kumra:** Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Writing – original draft, Writing – review & editing.

Declaration of competing interest

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Data availability

The data that has been used is confidential.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2024.100738.

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