

## Infections, Anti-infective Agents, and Risk of Deliberate Self-harm and Suicide in a Young Cohort: A Nationwide Study

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### ABSTRACT

**BACKGROUND:** Evidence links infections to mental disorders and suicidal behavior. However, knowledge is sparse regarding less severe infections, anti-infective treatment, and deliberate self-harm. Using nationwide Danish longitudinal registers, we estimated associations between infections treated with anti-infective agents and infections requiring hospitalization with the risk of deliberate self-harm.

**METHODS:** A total of 1.3 million people born between 1977 and 2002 were followed during the period from 1995 to 2013. In total, 15,042 individuals were recorded with deliberate self-harm (92% had been treated with anti-infective agents and 19% had been hospitalized for infections) and 114 died by suicide (64% had been treated with anti-infective agents and 13% had been hospitalized for infections). Hazard rate ratios were obtained while adjusting for age, gender, calendar period, education, hospitalizations with infections, prescribed anti-infective agents during childhood, parental mental disorders, and parental deliberate self-harm.

**RESULTS:** Individuals with infections treated with anti-infective agents had an increased risk of deliberate self-harm with a hazard rate ratio of 1.80 (95% confidence interval = 1.68–1.91). The associations fitted a dose–response relationship ( $p < .001$ ) and remained significant up to 5 years after last infection. An additive effect was found for individuals with an additional hospitalization for infections with an increased hazard rate ratio of 3.20 (95% confidence interval = 2.96–3.45) for deliberate self-harm.

**CONCLUSIONS:** An increased risk of deliberate self-harm was found among individuals with infections treated with anti-infective agents in temporal and dose–response associations. These results add to the growing literature on a possible link between infections and the pathophysiological mechanisms of suicidal behavior.

**Keywords:** Anti-infective agents, Deliberate self-harm, Infections, Inflammation, Primary care sector, Suicide

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Worldwide, suicide is a major health problem, with 800,000 people dying of suicide annually and an approximately 20-fold higher number of people committing deliberate self-harm (1). Among young people, suicide is one of the leading causes of death. While the term “suicidal behavior” covers both deliberate self-harm and death by suicide, these are not always seen as a continuum; actually, the majority of people who self-harm have no further episodes of suicidal behavior (2–4).

Mental disorders are linked to suicidal behavior (5). In addition, suicidal behavior might to some extent be mitigated through genetic disposition, either directly or through mental disorders (6). Nevertheless, there is a major need to identify novel and modifiable risk factors for suicidal behavior. Recently, multiple levels of evidence have pointed toward an immunological link with suicidal behavior (7). Specifically, production of certain inflammatory mediators appears to be upregulated in the brains of individuals who died by suicide (8–10) and in the cerebrospinal fluid of individuals with suicide attempts compared with healthy control subjects (11). In

addition, peripheral proinflammatory cytokine levels are increased among individuals with suicide attempts (12) and high suicidal ideation (13,14). These results are consistent with a recent meta-analysis reporting elevated levels of peripheral proinflammatory cytokines (15) and altered peripheral concentrations of pro- and anti-inflammatory markers in suicidal patients (16). In addition, infections and treatment with antibiotics can affect the gut microbiome, leading to behavioral alterations in animal models (17,18).

Of relevance, our recent nationwide cohort study noted an association between severe infections requiring hospitalization and risk of death by suicide (19). In addition, associations between infectious agents, such as *Toxoplasma gondii* and influenza B virus, and suicide attempts have previously been established in cross-sectional studies (20–24) and confirmed longitudinally in a large cohort study (25).

An accumulating body of research has shown that inflammation and infections are associated with mental disorders (26–32) and suicidal behavior (33–37). In addition, low-grade

SEE COMMENTARY ON PAGE 711

neuroinflammation might induce affective and behavioral dysregulation of the central nervous system, potentially leading to suicidality (38) with evidence of state-dependent elevation of the excitotoxic metabolite quinolinic acid in the cerebrospinal fluid (39), which could affect suicidal behavior. In addition, higher levels of the metabolite kynurenine were found in blood samples from patients with major depressive disorder and suicide attempts (40), and measures of kynurenine metabolites as a consequence of inflammation have been suggested to serve as biomarkers of suicide risk among individuals with suicide attempts compared with nonattempters (41). However, to date no large-scale study has investigated how individuals with less severe infections treated in the primary care sector might be linked to suicidal behavior.

Hence, the objective of the current study was to examine the association between infections treated with anti-infective agents and subsequent risk of deliberate self-harm. We furthermore tested for a potential dose–response relationship with respect to amount and type of anti-infective agents, including temporal associations. Finally, to include the severity of infections, we investigated the impact of infections requiring hospitalization on suicidal behavior.

## METHODS AND MATERIALS

### Danish Registers

A cohort design was applied. The current study used nationwide data from Danish registers where a unique personal identification number allows for complete linkage across databases. The Danish Civil Registration System (42) contains information on date of birth, gender, and parents. The Danish National Prescription Registry lists all prescriptions redeemed at Danish pharmacies after January 1, 1995. The Danish National Patient Register (43) and the Danish Psychiatric Central Research Register (44) contain information on all somatic hospital contacts since 1977 and psychiatric hospital contacts since 1969, respectively. Furthermore, both databases include outpatient and emergency room (ER) contacts since 1995. Diagnoses given during hospital contacts were recorded according to the International Classification of Diseases, 8th edition (ICD-8), until January 1, 1994, when the ICD-10 was introduced. The Registry of Causes of Death lists dates and causes of death. Finally, highest obtained educational level is listed in the Danish Education Register.

### Study Population

The study population consisted of all individuals born in Denmark between January 1, 1977, and December 31, 2002, followed from January 1, 1995, or their 10th birthday, whichever occurred last. We excluded those diagnosed with an infection during a hospital admission, ER contact, or outpatient consultation (see Supplemental Table S1), mental disorder (ICD-8 codes: 290–315; ICD-10 codes: F00–F99), or deliberate self-harm (defined below) prior to January 1, 1995, in order to restrict the sample to those with no previous incidences. The study population was considered at risk until outcome (see below), death, emigration, or end of the follow-up period on December 31, 2013, whichever came first.

### Exposure

The exposure of interest was prescribed anti-infective agents, as defined by the anatomical therapeutic chemical (ATC) codes in Supplemental Table S2. Prescriptions of anti-infective agents were used as a proxy for less severe infections treated in the primary care sector. We subdivided the sample into those exposed to 1) antibiotic agents, including antiseptics but excluding antibiotics for topical use and penicillin, 2) antiviral agents, 3) antimycotic agents, and 4) antiparasitic agents. Given that the majority of participants had been prescribed certain anti-infective agents, the reference group was set as individuals who had redeemed no prescription for anti-infective agents except for penicillin G (ATC code: J01CE01) and/or antibiotics for topical use (ATC code: D06A) because these medications are hypothesized to not affect the gastrointestinal system. To assess severity of the infections, antibiotics were subdivided into broad-spectrum, moderate-spectrum, narrow-spectrum, and topical antibiotics as listed in Supplemental Table S3. Individuals were considered as exposed from the date when a prescription for an anti-infective agent was redeemed. In addition, a time-varying covariate denoted whether individuals had hospital contact for infections during follow-up (see Supplemental Table S1). All types of hospitalizations were included (i.e., inpatient, outpatient, and ER).

### Outcome

The primary outcome was deliberate self-harm, defined as a somatic or psychiatric hospital contact (inpatient, ER, or outpatient) where deliberate self-harm had been recorded as the main diagnosis or subdiagnosis (ICD-8 codes: 590–595; ICD-10 codes: X60–X84, Y87). Death by suicide was examined as a secondary outcome and identified in the Cause of Death Register using the ICD codes listed above.

### Statistical Analysis

First, we compared exposed individuals with those in the reference group with respect to risk of deliberate self-harm. Second, we determined whether the risk differed with respect to type of anti-infective agents, number of redeemed prescriptions with anti-infective agents, and time since the last prescription. Similarly, we assessed whether risk varied with respect to hospitalizations with infections or mental disorders. We constructed Cox regressions using age as the underlying time scale and obtained hazard rate ratios (HRRs) with 95% confidence intervals (95% CIs). The proportional hazard assumptions were tested based on Schoenfeld's residuals. The assumption was not violated in any examined models. The Wald test was used to assess for significant differences between risk estimates. All analyses were adjusted for age, gender, calendar period, education (primary school, secondary school, vocational education, short higher education, medium long higher education, or a university degree), hospitalizations with infections after January 1, 1995, prescribed anti-infective agents during the first years of life (6 months, 6–12 months, and 1–10 years) because these are vulnerable periods of brain development (possible only for those with information during these age periods after January 1, 1995), parental mental disorders, and parental deliberate self-harm. These were included as time-varying covariates where possible.

Finally, we calculated the population attributable risk for deliberate self-harm, which is the theoretical fraction of the total number of deliberate self-harm cases that would not have occurred if the association with infections requiring treatment with anti-infective agents was causal and could be eliminated. The formula was as follows:  $PAR = (HRR_e - 1) / [1 + P_e (HRR_e - 1)]$ , where PAR is population attributable risk,  $P_e$  is the prevalence of exposure, and  $HRR_e$  is the HRR of disease due to that exposure.

### Sensitivity Analyses

First, we used a reference group containing individuals with no prescriptions or one prescription for anti-infective agents. Second, we stratified the sample into individuals with and without any diagnosed mental disorders (ICD-10 codes: F00–F99) while accounting for date of diagnosis. Third, we included individuals treated with penicillin G in the exposure group.

All analyses were performed with STATA version 14.0 (StataCorp LP, College Station, TX). The study was approved by the Danish Data Protection Agency and the Danish Health Data Authority.

## RESULTS

### Baseline Characteristics

We identified 1,358,578 individuals (672,775 [49.5%] women and 685,803 [50.5%] men) who were born between 1977 and 2002 and had not previously been hospitalized due to infections, mental disorders, or deliberate self-harm. A total of 2098 individuals were excluded owing to a mental disorder diagnosis prior to January 1, 1995. Furthermore, a total of 27,449 individuals emigrated during the study period. These 1,358,578 individuals were observed over a total of 4,182,067 person-years from 1995 to 2013 (mean age of 21.5 years, SD = 7.4, by the end of follow-up). During follow-up, a total of 16,108 individuals were diagnosed with a mood disorder (ICD-10 code: F3), 4826 were diagnosed with a substance abuse disorder (ICD-10 code: F1), and 6346 were diagnosed with a personality disorder (ICD-10 code: F6).

A total of 15,042 individuals (359.7/100,000 person-years) were recorded with an episode of deliberate self-harm (median age of 18.4 years, SD = 4.4; 68.2% women). Of these, 13,800 individuals (91.7%) had previously been treated with anti-infective agents and 2807 (18.7%) had previously been hospitalized with infections. In all, 114 individuals (2.7/100,000 person-years) died by suicide (median age of 18.9 years, SD = 2.8; 18.4% women). Among these, 73 (64.0%) had previously been treated with anti-infective agents and 15 (13.2%) had previously been hospitalized with infections.

### Risk of Deliberate Self-harm

Individuals treated with anti-infective agents had an increased HRR of deliberate self-harm, 1.80 (95% CI = 1.68–1.91), when compared with the reference group of nontreated individuals (Table 1). Particularly antibiotics (HRR = 1.84, 95% CI = 1.71–2.00) were associated with increased risk of deliberate self-harm; broad-spectrum antibiotics yielded the highest risk ( $p < .01$  for comparison). With respect to the number of

**Table 1. HRRs of Deliberate Self-harm According to Type of Anti-infective Agents Among Individuals Born in Denmark Between 1977 and 2002**

Anti-infective Agent	Deliberate Self-harm	
	Number of Cases (%)	HRR <sup>a</sup> (95% CI)
Total	15,042 (100)	
No Anti-infective Prescription	1242 (8.3)	1.00 (reference)
Any Anti-infective Prescription	13,800 (91.7)	1.80 (1.68–1.91)
Antibiotics	13,549 (90.1)	1.84 (1.71–2.00)
Broad spectrum <sup>b</sup>	4904 (32.6)	1.69 (1.63–1.75)
Moderate spectrum <sup>b</sup>	4950 (32.9)	1.44 (1.39–1.50)
Narrow spectrum <sup>b</sup>	10,501 (69.8)	1.54 (1.48–1.60)
Topical <sup>b</sup>	5653 (37.6)	1.33 (1.28–1.37)
Antivirals	1814 (12.1)	1.24 (0.86–1.79)
Antimycotics	5426 (36.1)	1.11 (0.93–1.32)
Antiparasitics	3363 (22.4)	1.28 (0.99–1.65)

CI, confidence interval; HRR, hazard rate ratio.

<sup>a</sup>The analyses were adjusted for age, gender, calendar period, education, hospitalizations with infections after 1995, prescribed anti-infective agents during childhood (available since 1995), parental mental disorders, and parental deliberate self-harm.

<sup>b</sup>The categorization into the different types of antibiotics is provided in Supplemental Table S3. The analyses of the different anti-infective agents were mutually adjusted for treatment with other anti-infective agents and, thus, are comparable across agent types.

redeemed prescriptions, a dose–response relationship was noted ( $p < .0001$ ) (Table 2). We also noted a temporal association with a peak in risk during the first year after last redeemed prescription; the elevated risk remained significant until 5 years after last redeemed prescription ( $p < .0001$ ) (Table 3).

Infections requiring hospitalization were associated with the highest risk of deliberate self-harm with an HRR of 3.20 (95% CI = 2.96–3.45), and a dose–response relationship with the number of prescriptions provided from primary care settings was noted (Figure 1). However, individuals who had only been treated with anti-infective agents in primary care settings also showed an elevated risk (HRR = 1.79, 95% CI = 1.67–1.91),  $p < .001$  for comparison. The population attributable risk of deliberate self-harm associated with those with infections treated with any anti-infective agents was 47%.

### Risk of Death by Suicide

Anti-infective agents were associated with a nonsignificant increased risk of death by suicide (HRR = 1.30, 95% CI = 0.85–1.97). Having been hospitalized for infections was linked to a significantly higher risk of suicide with an HRR of 3.13 (95% CI = 1.67–5.87). Because of the low number of suicide deaths in this young cohort, it was not feasible to explore this outcome further.

### Sensitivity Analyses

Comparable risk estimates were found when broadening the reference group to include individuals with no prescriptions or one prescription of anti-infective agents; two or more

**Table 2. HRRs of Deliberate Self-harm According to Number of Redeemed Prescriptions With Anti-infective Agents Among Individuals Born in Denmark Between 1977 and 2002**

Number of Prescriptions for Anti-infective Agents	Deliberate Self-harm	
	Number of Cases (%)	HRR <sup>a</sup> (95% CI)
Total	15,042 (100)	
No Anti-infective Prescription	1242 (8.3)	1.00 (reference)
Any Anti-infective Prescription	13,800 (91.7)	1.80 (1.68–1.91)
1	2521 (16.8)	1.34 <sup>b</sup> (1.24–1.44)
2–4	4219 (28.1)	1.90 <sup>b</sup> (1.77–2.05)
5–9	3835 (25.5)	2.57 <sup>b</sup> (2.38–2.78)
10–19	2313 (15.4)	2.77 <sup>b</sup> (2.54–3.01)
20+	912 (6.1)	3.02 <sup>b</sup> (2.74–3.35)
Number of Different Anti-infective Agents <sup>c</sup>		
0	1242 (8.3)	1.00 (reference)
1	6344 (42.2)	1.71 <sup>b</sup> (1.59–1.83)
2	4966 (33.0)	2.01 <sup>b</sup> (1.87–2.17)
3	2140 (14.2)	2.47 <sup>b</sup> (2.27–2.69)
4	364 (2.4)	2.46 <sup>b</sup> (2.16–2.80)

CI, confidence interval; HRR, hazard rate ratio.

<sup>a</sup>The analyses were adjusted for age, gender, calendar period, education, hospitalizations with infections after 1995, prescribed anti-infective agents during childhood (available since 1995), parental mental disorders, and parental deliberate self-harm.

<sup>b</sup>The results on the amount of anti-infective agents and number of different anti-infective agents fitted a dose–response relationship ( $p < .0001$ ) tested with the Wald’s test.

<sup>c</sup>This was included to have a measure for the diversity and severity of infections and treatments, that is, to include individuals with prescriptions for several of the four groups of anti-infective agents (i.e., antibiotics, antivirals, antimycotics, and antiparasitics).

infections treated with anti-infective agents increased the risk of deliberate self-harm by an HRR of 1.77 (95% CI = 1.70–1.85) (see Supplemental Table S4). With this broader reference group, we found a dose–response relationship to infections treated with anti-infective agents as well as temporal associations (all  $ps < .001$ ; results not shown).

Among those with a deliberate self-harm episode, 7053 individuals (46.9%) had previously been diagnosed with a

**Table 3. HRRs of Deliberate Self-harm According to Time Since Last Prescription With Anti-infective Agents Among Individuals Born in Denmark Between 1977 and 2002**

Time Since Last Prescription With Anti-infective Agents	Deliberate Self-harm	
	Number of Cases (%)	HRR <sup>a</sup> (95% CI)
Total	15,042 (100)	
No Anti-infective Prescriptions	1242 (8.3)	1.00 (reference)
0–3 Months	2783 (18.5)	1.85 (1.75–1.96)
3–6 Months	1602 (10.7)	1.83 (1.73–1.95)
6–12 Months	2078 (13.8)	1.71 (1.61–1.82)
1–2 Years	2344 (15.6)	1.53 (1.44–1.64)
2–5 Years	3160 (21.0)	1.37 (1.28–1.46)
5–10 Years	1575 (10.5)	1.08 (0.99–1.19)
≥10 Years	258 (1.7)	1.08 (0.84–1.39)

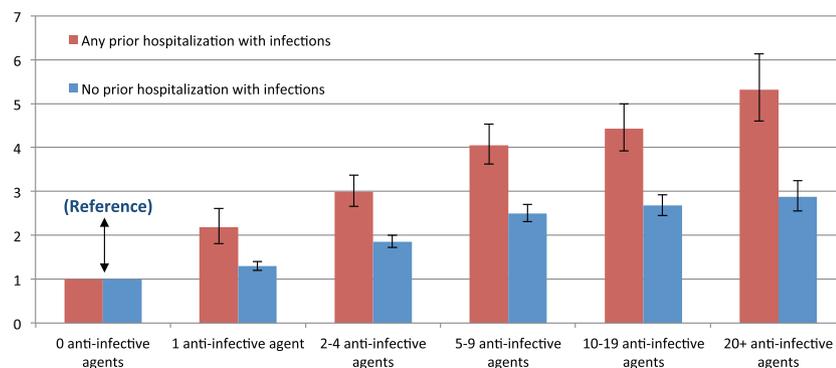
CI, confidence interval; HRR, hazard rate ratio.

<sup>a</sup>The analyses were adjusted for age, gender, calendar period, education, hospitalizations with infections after 1995, prescribed anti-infective agents during childhood (available since 1995), parental mental disorders, and parental deliberate self-harm.

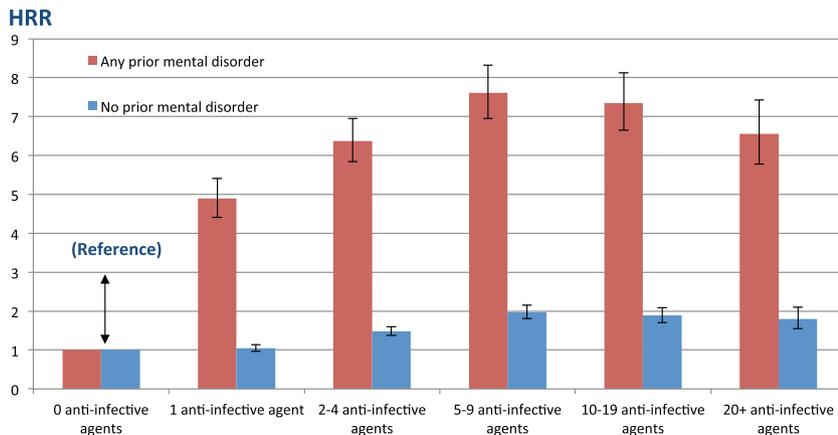
mental disorder. Of these, 6709 (95.1%) had been treated with anti-infective agents before being diagnosed with a mental disorder. Compared with individuals with no mental disorders or prior treatment for infections, individuals with a history of mental disorder and infections treated with anti-infective agents had an HRR of 6.30 (95% CI = 5.84–6.79). However, individuals with no prior mental disorder but treated with anti-infective agents also displayed an elevated risk of deliberate self-harm (HRR = 1.39, 95% CI = 1.29–1.50),  $p < .0001$ . In addition, a dose–response relationship was noted here (all  $ps < .0001$ ) (Figure 2).

Among individuals diagnosed with a mental disorder prior to death by suicide ( $n = 20$ ), those with infections treated with anti-infective agents had an HRR of 2.42 (95% CI = 1.29–4.53), while individuals with no history of mental disorders had a ratio of 1.17 (95% CI = 0.76–1.80),  $p = .018$ . Lastly, we conducted a round of sensitivity analysis where individuals treated with penicillin G were included in the exposure group; this did not change the overall finding.

**HRR**



**Figure 1.** Hazard rate ratios (HRRs) of deliberate self-harm according to number of redeemed prescriptions with anti-infective agents among individuals born in Denmark between 1977 and 2002 divided by persons with and without any prior hospitalizations with infections since 1995. We performed Cox regression analyses presenting HRRs with 95% confidence intervals. All analyses were adjusted for age, gender, calendar period, education, parental mental disorders, parental deliberate self-harm, anti-infective use during childhood, and hospitalizations with infections after 1995. The linear trend between the number of anti-infective agents and the risk of deliberate self-harm was significant in both groups ( $p < .0001$ ).



**Figure 2.** Number of redeemed prescriptions for anti-infective agents and the risk of deliberate self-harm among persons born between 1977 and 2002 divided by individuals with and without any prior mental disorder since 1995. We performed Cox regression analyses presenting hazard rate ratios (HRRs) with 95% confidence intervals. All analyses were adjusted for age, gender, calendar period, education, parental mental disorders, parental deliberate self-harm, anti-infective use during childhood, and hospitalizations with infections after 1995. The linear trend between the number of anti-infective agents and the risk of deliberate self-harm was significant in both groups ( $p < .0001$ ).

## DISCUSSION

To our knowledge, this is the largest study to investigate the association between less severe infections treated with anti-infective agents and subsequent risk of deliberate self-harm or death by suicide using nationwide data. By studying more than 1.3 million people, we found an 80% higher risk of deliberate self-harm among individuals with infections treated with anti-infective agents. A dose-response relationship was noted with respect to number of prescribed anti-infective agents, and the increased risk of deliberate self-harm persisted for up to 5 years after last prescription. With respect to type of agent, the highest risk was observed for individuals treated with broad-spectrum antibiotics. An excess risk of deliberate self-harm was also found for individuals who had been hospitalized for infections. No significant risk was noted for antivirals, antimycotics, or antiparasitic agents, possibly owing to low exposures; furthermore, infections treated with antibiotics might be more severe than those treated with antivirals, antimycotics, or antiparasitic agents. In addition, treatment with antibiotics, especially broad-spectrum antibiotics, is likely to affect the microbiome to a greater extent (45).

Previous research has linked inflammation to suicidal behavior (8–10) and has shown an increased risk of suicide among persons hospitalized with infections (19). This study adds to the existing body of evidence by using a different proxy for infections, prescriptions on anti-infective agents, albeit finding only a trend toward an increased risk of suicide. The lack of significance could be related to the relatively fewer cases of suicide in this young cohort or the difference in severity of the infection. All estimates were adjusted for important risk factors for suicidal behavior, including age, gender, calendar period, education, infections during childhood, parental mental disorders, and deliberate self-harm among parents. Our main results remained significant when replacing the reference group with one consisting of individuals prescribed no prescriptions or only one prescription of anti-infective agents, which might represent the background population to a greater extent.

Our findings suggest that less severe infections treated with anti-infective agents play a relevant role in the pathophysiological mechanisms of suicidal behavior. This supports the

hypothesis that suicidal behavior can be predisposed, triggered, or perpetuated by infections (19,20,25) or immune activation secondary infections (15,16). Furthermore, it is increasingly recognized that infections and inflammation are linked to mental disorders (26–32). In addition, a link between the immune system and genes coding for mental disorders has been suggested (46), which could explain a higher risk of infections among individuals with mental disorders. Moreover, triggers of inflammation such as autoimmunity, stress, and brain injury may contribute to the pathophysiology of deliberate self-harm and suicide (36). In our study, as expected, individuals diagnosed with mental disorders had a higher risk of deliberate self-harm compared with individuals not diagnosed. Yet, we still found a significantly increased risk of deliberate self-harm among individuals treated with anti-infective agents but with no diagnosed mental disorders. Moreover, the gut microbiome is extremely sensitive to anti-infective agents, and there is a growing body of evidence, based on studies of rodent and humans, supporting the notion that the microbiome may exert neuromodulatory effects on both brain function and behavior (17,18). Recent evidence has incriminated links between infections treated with antibiotics and major mental illnesses (26). Nevertheless, to our knowledge, it was impossible to tease apart the effects of indication (infection) or anti-infective medication; that is, both infections and treatment with anti-infective agents may explain, fully or in part, the observed associations. Hence, infections (directly or via immune activation) as well as the treatment with anti-infective agents (via diminished microbiome-dependent immune regulation), together with genetic vulnerability factors, could lead to disturbances within the immune system and subsequently to deliberate self-harm in certain subgroups of the population. Furthermore, immune dysregulation [induced by certain infections and their treatment and priming of the brain microglia by peripheral infections (47)] can lead to increased vulnerability to later infections, with a temporal amplifying effect. This slow-moving cascading effect might explain the high population attributable risk of 47%, that is, the theoretical proportion of deliberate self-harm that might be prevented if the studied association was causal and could be eliminated. Still, a wide range of mechanisms might affect

emotion and behavior, including risk-taking behaviors such as drug use, risk-taking sexual behavior, and poor diet. In addition, stressful life events or mental disorders might explain parts of the observed association and contribute to the very high attributable risk. These factors might also act as mediators by affecting the immune system and increase susceptibility to infections, leading to prescriptions of anti-infective agents. Indeed, even before diagnosis of the first episode of psychosis, people were found to have more frequent contacts with general practitioners years before being diagnosed with schizophrenia (48). Being prescribed anti-infective agents in the primary care sector may be a proxy for help-seeking behavior among individuals at risk for suicide and thus may be a marker rather than a potential cause of suicidal behavior. With these confounding and modifying factors in mind, we still found a significantly increased risk of deliberate self-harm among individuals with infections treated with anti-infective agents after excluding all individuals with previous records of deliberate self-harm and mental disorders prior to 1995 and after adjusting for educational level and parental mental disorders and deliberate self-harm among parents. Hence, our findings underline the importance of early identification and treatment of infections as well as the need for research on the pathophysiological mechanisms underlying the link among infectious diseases, their treatment, and deliberate self-harm, in particular among young individuals.

### Strengths and Limitations

Strengths of this study include nationwide data covering more than 1.3 million individuals with complete follow-up. Data were collected prospectively in an unbiased manner, and the risk estimates were adjusted for time-varying covariates, adding precision to the estimates. Concerning limitations, although we did include all infections requiring treatment with anti-infective agents or requiring hospitalization, we could not account for untreated infections, compare specific infections, or address heterogeneity related to wide inclusion criteria. Although diagnoses of infections would have been preferred, these are not available from the primary care sector in Denmark (49); hence, nationwide data on prescriptions of anti-infective agents were used as a proxy for less severe infection. This approach has previously been employed (26). Redeemed prescriptions were also just a proxy for actual use of anti-infective medications because no information on actual consumption of anti-infective agents was available, yet mean adherence of 62.2% after redeemed prescriptions was previously reported (50). Furthermore, owing to the young age of this cohort, we observed relatively few deaths by suicide, limiting its potential as an outcome. Finally, mental disorders and psychiatric symptoms might act as mediators in the association between infections and risk of deliberate self-harm and suicide. In addition, reverse causality is a limitation in register-based studies because the link between infections and mental disorders or intense stress often preceding suicidal behavior could be bidirectional (51). Furthermore, mental disorders might go undiagnosed, and deliberate self-harm is known to be underrecorded (52). Most cases with mild to moderate mental disorders, including anxiety, affective, and personality disorders, are treated by general practitioners or specialists in

psychiatry working in private practices and therefore not included in the current study. On the other hand, there are no private psychiatric hospitals in Denmark; thus, we have a complete and nationwide registration of individuals diagnosed with severe mental disorders requiring hospitalization (44). In addition, chronic somatic illnesses might be a potential limitation in this study, but owing to the relatively young age of this cohort, the majority were likely medically healthy young adults.

### Conclusions

In this large-scale prospective nationwide cohort study, we found a significantly increased risk of deliberate self-harm among individuals with infections treated with anti-infective agents in both temporal and dose–response predictive associations, robust to adjustment for a range of possible confounders. In addition, having been hospitalized with infection nearly doubled the risk, indicating that level of severity is linked to risk of deliberate self-harm. Although our study cannot provide evidence on the underlying causal mechanisms, these results support the importance of early identification and need for research on how infections affect the pathophysiology of suicidal behavior. Future large longitudinal studies may include genotype and gene expression data to better understand individual vulnerability to behavioral dysregulation and symptomatic exacerbation induced or perpetuated by infection. Furthermore, prospective clinical studies following psychiatric patients after an acute infection are warranted to evaluate whether infections elevate the short-term suicide risk. Interventional paradigms may help to assess whether the association can be explained through direct effects of infection, immune responses to infection, treatment with anti-infective agents through diminished immunoregulation or gut–brain mechanisms, or interactive combinations of all three factors. Causal inference methods nested in epidemiology, such as marginal structural modeling, could be used for that purpose. Ultimately, these efforts could contribute to a broader understanding and better prediction and management of suicidal behavior.

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OK-F and LP had full access to, and take responsibility for the integrity of, the data and analysis. All information and materials in the manuscript are original.

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## Infections and Risk of Deliberate Self-harm and Suicide

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