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SHORT COMMUNICATION

Diabetes Mellitus Type 2 as a Risk Factor and Outcome Modifier for Cryptococcosis in HIV Negative, Non-transplant Patients, a Propensity Score Match Analysis

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Abstract

Cryptococcosis is an opportunistic fungal infection of worldwide distribution with significant associated morbidity and mortality. HIV, organ transplantation, malignancy, cirrhosis, sarcoidosis, and immunosuppressive medications are established risk factors for cryptococcosis. Type 2 diabetes mellitus (DM2) has been hypothesized as a risk factor and an outcome modifier for cryptococcosis. We aimed to compare outcomes among HIV-negative, non-transplant (NHNT) patients with and without DM2. We queried a global research network to identify NHNT patients ($n=3280$). We performed a propensity score-matched (PSM) analysis comparing clinical outcomes among cryptococcosis patients by DM status. We also characterize adults with cryptococcosis and DM2 as the only risk factor. After PSM, NHNT patients with DM2 were more likely to develop cognitive dysfunction [9% vs. 6%, OR 1.6; 95% CI (1.1–2.3); $P=0.01$] but had similar mortality, hospitalization, ICU, and stroke risk after acquiring cryptococcosis when compared to NHNT patients without DM2. Pulmonary cryptococcosis was the most common site of infection. Among 44 cryptococcosis patients with DM2 as the only identifiable risk factor for disease, the annual incidence of cryptococcosis was 0.001%, with a prevalence of 0.002%. DM2 is associated with increased cognitive dysfunction risk in NHNT patients with cryptococcosis. It is rare for DM2 to be the only identified risk factor for developing cryptococcosis. Kidney disease, hyperglycemia, and immune dysfunction can increase the risk of cryptococcosis in patients with DM2.

Introduction

Cryptococcosis is an opportunistic fungal infection of worldwide distribution. Two species are responsible for human infections: *Cryptococcus neoformans* and, less commonly, *Cryptococcus gattii*. The disease can be classified according to the affected anatomical location, including pulmonary, cerebral, cutaneous, skeletal, and disseminated infections. Clinical presentation varies with the anatomic location of the infection, and the immunological status of the host [1–4].

Although cryptococcosis can occur in either immunocompromised or immunocompetent patients,

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immunocompromised patients are at higher risk for developing life-threatening complications and worse disease. Immunosuppressive comorbidities, such as advanced HIV, organ transplantation, malignancy, cirrhosis, sarcoidosis, and immunosuppressive medications, are established risk factors for cryptococcosis [5, 6]. Delayed diagnosis of cryptococcosis, allowing the development of complications such as lacunar strokes or worsened meningoencephalitis, can occur in immunocompetent persons with underrecognized risk factors for infection. The World Health Organization (WHO) lists *Cryptococcus neoformans* as a critical priority fungal pathogen.

Diabetes mellitus type 2 (DM2) may be a risk factor for worse cryptococcosis outcomes due to several overlapping factors. A hyperglycemic state is known to impair essential functions of the immune system, such as polymorphonuclear leukocyte chemotaxis, phagocytosis, and cell-mediated immunity. Furthermore, paradoxically increased TNF-alpha and interleukin-6 (IL-6) levels in diabetic patients can be associated with an impaired immune response to *Cryptococcus,* leading to unfavorable outcomes [7–10]. We previously found an association between increased mortality of pulmonary cryptococcosis and uncontrolled diabetes mellitus [11], and severity remains high among those patients [12]. Although common in the general population, it is unclear what role diabetes mellitus plays in developing cryptococcosis and how it may modulate cryptococcosis outcomes. We aimed to compare outcomes among HIV-negative, non-transplant (NHNT) patients with and without DM2. We also characterize a cohort of patients with cryptococcosis and DM2 who had no other identifiable risk factors.

Materials and Methods

Global Federated Research Network

The TriNetX global research network database was queried to identify adult patients with cryptococcosis diagnoses based on the ICD-10 code (B45) or specific Cryptococcosis lab results in December 2022. TriNetX has global data for approximately 100 million patients from more than 80 medical centers in the US, Canada, Europe, Australia, Indonesia, and other countries. Our group has published several reports using the same platform [13–15]. Each contributing Healthcare organization (HCO) delivers electronic medical record (EMR) systems data collected to provide patient care. Received data are either structured or unstructured data processed by Natural Language Processing Technology. Most participating healthcare organizations are large academic medical institutions with inpatient and outpatient facilities. The data they provide represent the entire patient population at the healthcare organization. Most give an average of seven years of historical data. TriNetX receives data directly from a healthcare organization research repository into the TriNetX environment, or the HCO sends TriNetX data extracts in the form of CSV files coded in the TriNetX Data Dictionary. HCO and other data providers update their data at various times, with over 80% refreshing in 1-, 2-, or 4-week frequency intervals. The average lag time for a healthcare organization's source data to refresh is one month. TriNetX maps the data to a standard, controlled set of clinical terminologies and transforms it into a proprietary data model. This transformation process includes extensive data quality assessment that includes data cleaning that rejects records that do not meet the TriNetX quality standards.

TriNetX is certified to the ISO 27001:2013 standard and maintains an Information Security Management System (ISMS) to ensure the protection of the healthcare data it has access to and to meet the requirements of the HIPAA Security Rule. Any data displayed on the TriNetX Platform in aggregate form, or any patient-level data provided in a data set generated by the TriNetX Platform, only contain de-identified data as per the de-identification standard defined in Section §164.514(a) of the HIPAA Privacy Rule. The process of de-identifying data is attested to through a formal determination by a qualified expert as defined in Section §164.514(b)(1) of the HIPAA Privacy Rule. Geographic reporting at the regional level prevents potential re-identification through the localization of patients or HCOs.

Study Design and Population

The majority (86%) of patients in this database are from the United States of America. Cryptococcosis was defined by ICD codes, a positive PCR test, positive antigen results in blood or cerebrospinal fluid, or an antigen titer > 1:32 in serum or cerebrospinal fluid (Supplementary File).

We first identified NHNT patients diagnosed with cryptococcosis within five years based on ICD-10 codes or laboratory results (Supplementary File). These patients were divided into two cohorts by the presence ($N = 995$) or absence ($N = 2285$) of DM2 by the ICD code E11. Index events were DM2 or a visit within TriNetX, respectively.

We then described a cohort of patients diagnosed with cryptococcosis within five years after diagnosis of DM2 ($N = 44$). We excluded from this cohort persons with ICD-10 diagnoses of other major risk factors for cryptococcosis, including the use of immunosuppressants, cirrhosis, aplastic anemias, neoplasms, HIV, systemic lupus erythematous, and transplant recipients.

Demographic characteristics, comorbidities, medications, and laboratory tests (see Supplementary Data Tables S1–S4) were non-time bound captured before the index event for each cohort.

Global Federated Research Network Outcome Measures

The primary outcome studied was the mortality rate at one year following the diagnosis of cryptococcosis. The secondary outcomes studied were hospitalization rates, intensive care unit (ICU) admission, mechanical ventilation, and stroke or cognitive dysfunction development within one year of cryptococcosis diagnosis. Outcomes were defined by ICD-10 code diagnosis or Current Procedural Terminology (CPT) codes (Supplementary Tables S1 and S4). This analysis included outcomes within the same day of a cryptococcosis diagnosis and up to 365 days after a cryptococcosis diagnosis.

Incidence/Prevalence Analysis

The incidence and prevalence analyses for cryptococcosis diagnosis were performed using the TriNetX platform from January 1, 2020, to December 31, 2022. We sampled all patients with DM2 as the only risk factor who were ≥ 18 years of age.

Statistical Analysis

Statistical analyses of data obtained from the global federated research network were completed on the TriNetX platform. Descriptive statistics were reported as means and standard deviations for continuous variables and as frequency and percentages for categorical variables. Outcomes were reported after propensity score matching. Propensity score matching was performed for age, sex, race, ethnicity, and specific comorbidities. The matched comorbidities were chronic kidney disease (CKD) (N18), aplastic anemias (D60–D64), ischemic heart disease (I20-25), liver fibrosis (K74), systemic connective tissue disorders (M30–M36), neoplasm (C00-D49), and glucocorticoids. Propensity score matching was performed using a 1:1 greedy nearest-neighbor algorithm utilizing a caliper width of 0.1 pooled standard deviations (SD0). Balance on covariates was assessed using standardized mean difference, and absolute values > 0.1 were considered positive for residual imbalance. All analyses were done in the TriNetX platform.

Data Access

The corresponding author had full access to data in the study and had final responsibility for the decision to submit the manuscript for publication. The datasets generated and analyzed in the current study are available from the corresponding author upon request.

Ethics Statement

Research utilizing TriNetX does not require ethical approval, as patient-identifiable information is not accessible to users. The current project is in Health Insurance Portability and Accountability Act (HIPAA) compliance, according to the Colorado Multiple Institutional Review Board (COMIRB) at the University of Colorado in Denver. Analysis of clinical data was performed under an approved protocol (COMIRB Protocol 15-1340).

Results

Comparison of NHNT Patients with Cryptococcosis, With or Without DM2

We analyzed 3280 NHNT patients diagnosed with cryptococcosis. To assess outcomes, we divided them into patients with ($n = 995$) and without ($n = 2285$) DM2. Cohorts had similar baseline demographics for age and sex. NHNT patients with DM2 had higher rates of obesity ($P < 0.001$), hyperlipidemia ($P < 0.001$), hypertensive diseases ($P < 0.001$), ischemic heart disease ($P < 0.001$), heart failure ($P < 0.001$), chronic kidney disease ($P < 0.001$), liver fibrosis or cirrhosis ($P < 0.001$), and aplastic anemia or other bone marrow failure ($P < 0.001$), when compared to NHNT patients without DM2 before matching. NHNT patients with DM2 had a mean serum glucose of 140.5 mg/dL and a mean hemoglobin A1c of 7.3%. The use of glucocorticoids, including prednisone and dexamethasone, was higher in the cohort of NHNT patients with DM2, as were other immune suppressants (Table 1). If the ICD-10 code specified an anatomic site of infection, the most common place for all cohorts was pulmonary, followed by cerebral (Table 2).

Outcome Analysis

After propensity score matching, 793 patients remained in each cohort. NHNT patients with DM2 had higher rates of hypertension (77.3% vs. 52%, $P < 0.0001$), hyperlipidemia (47% vs. 26%, $P < 0.0001$), and obesity (24% vs. 13%, $P < 0.0001$). Pulmonary, cerebral, and disseminated cryptococcosis rates were similar among both groups.

At one year, NHNT patients with DM2 had similar rates of mortality [OR 0.9; 95% CI: (0.7–1.1); $P = 0.182$], hospitalization [OR 1.1; 95% CI (0.9–1.4); $P = 0.09$], and ICU admission [OR 1.2; 95% CI (0.9–1.5); $P = 0.127$], compared to NHNT patients without DM2 (Fig. 1). NHNT patients with DM2 were more likely to develop cognitive dysfunction [OR 1.6; 95% CI (1.1–2.3); $P = 0.01$], but not stroke

Table 1 Clinical characteristics of patients with cryptococcosis by risk factors

Clinical characteristics *N* (%), mean ± SD	NHNT with DM2 (*n* = 995) *n* (%)	NHNT without DM2 (*n* = 2285) *n* (%)	DM2 only (*n* = 44) *n* (%)
Demographics			
Age	61.2 ± 12	54.4 ± 16	58.9 ± 12
Male	559 (57.6)	1312 (63.1)	25 (64.1)
White	604 (62.3)	1305 (62.8)	24 (61.5)
Black or African American	149 (14.7)	332 (15.0)	10 (25.6)
Hispanic or Latino	142 (14.6)	178 (8.6)	10 (25.6)
Asian	20 (2.0)	46 (2.0)	10 (25.6)
Native Hawaiian or PI	0 (0)	< 10 (0)	0 (0)
Diagnoses (ICD-10 codes)			
Hypertensive diseases	588 (60.6)	467 (22.5)	11 (28.2)
Hyperlipidemia	488 (49)	343 (15)	11 (28.2)
Neoplasms	376 (38.8)	549 (26.4)	0 (0)
Aplastic anemias	341 (35.2)	298 (14.3)	0 (0)
DM2 with hyperglycemia	348 (35)	0 (0)	12 (27)
Ischemic heart disease	338 (34)	274 (12)	12 (27)
Chronic kidney disease	267 (27.5)	153 (7.4)	10 (25.6)
End-stage renal disease	82 (8.5)	42 (2.0)	10 (25.6)
Overweight, obesity	204 (21.0)	112 (5.4)	10 (25.6)
Heart failure	187 (19.3)	117 (5.6)	10 (25.6)
Liver fibrosis or cirrhosis	126 (13.0)	103 (5.0)	0 (0)
Connective tissue disorders	76 (7.8)	97 (4.7)	0 (0)
Pulmonary fibrosis	35 (3.6)	63 (3.0)	0 (0)
Hydrocephalus	33 (3.4)	45 (2.2)	0 (0)
Sarcoidosis	33 (3.4)	44 (2.1)	0 (0)
Tuberculosis	12 (1.2)	15 (0.7)	0 (0)
Cystic fibrosis	10 (1.0)	10 (0.5)	0 (0)
Laboratory findings			
Hemoglobin A1c (%)	7.3 ± 2.1	5.9 ± 1.5	6.6 ± 2.2
Hemoglobin [mg/dL]	11.2 ± 2.6	11.7 ± 2.5	12.9 ± 2.6
Hematocrit [%]	34.1 ± 7.5	35.2 ± 7.5	39.7 ± 6.6
Platelets [10^3/μL]	214.8 ± 117.5	228.5 ± 116.9	230.4 ± 90.2
Leukocytes [10^3/μL]	8.4 ± 4.5	9.4 ± 4.5	9.8 ± 4.4
Lymphocytes [10^3/μL]	18.4 ± 14.9	19.3 ± 15.2	19.4 ± 9.9
Glucose [mg/dL]	140.5 ± 68	107.6 ± 31.5	183.2 ± 92.4
LDH [units/L]	285.4 ± 252.4	338.0 ± 536.6	254.3 ± 340.6
Ferritin [ng/ml]	910 ± 4241	724 ± 1042	31 ± 0
C-reactive protein [mg/L]	32.1 ± 55	36.8 ± 61	12.9 ± 12
Medications			
Glucocorticoids	439 (45.3)	679 (32.7)	0 (0)
Prednisone	227 (23.4)	328 (15.8)	0 (0)
Dexamethasone	181 (18.7)	289 (13.9)	0 (0)
Immunosuppressants[a]	82 (8.5)	100 (4.8)	0 (0)
Rituximab	17 (1.8)	30 (1.4)	0 (0)
Tocilizumab	14 (1.4)	10 (0.5)	0 (0)
Alemtuzumab	10 (1.0)	0 (0)	0 (0)

Non-HIV non-transplant (NHNT) patients were sorted into patients with or without DM2. A cohort was identified of patients with DM2, with the exclusion of patients with any other identified risk factors for cryptococcosis (DM2 only). *PI* Pacific islander, *LDH* lactate dehydrogenase

[a]Immunosuppressants included: Tacrolimus, Mycophenolate mofetil, Mycophenolic acid, Cyclosporine, Azathioprine, Sirolimus, Infliximab, Basiliximab, Belatacept, Omalizumab, Siltuximab, Belumosudil, Ustekinumab

Table 2 Cryptococcosis ICD-10-based diagnosis, stratified by anatomic site of infection

Anatomic site of cryptococcosis *n* (%)	NHNT with DM (*n* = 995)	NHNT without DM (*n* = 2285)	DM2 only (*n* = 44)
Cryptococcosis (B45)	907 (92)	1900 (83.2)	38 (86.4)
Unspecified (B45.9)	484 (48.6)	1004 (43.9)	22 (50)
Pulmonary (B45.0)	470 (47.2)	1005 (44)	22 (50)
Disseminated (B45.7)	349 (35.1)	720 (31.5)	16 (36.4)
Cerebral (B45.10)	352 (35.1)	720 (31.5)	18 (40.9)

NHNT Non-HIV, non-transplant (NHNT) patients; *DM2* diabetes mellitus type 2

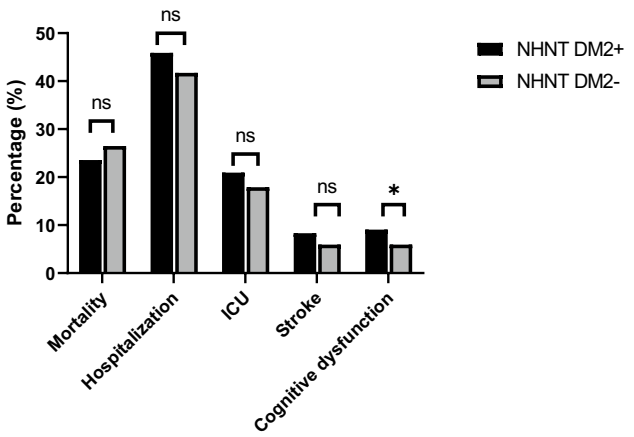

Fig. 1 Graphical analysis of outcomes among NHNT patients with cryptococcosis, with versus without DM2. *NHNT* Non-HIV, non-transplant (NHNT) patients; *DM2* diabetes mellitus type 2. *ICU* Intensive care unit. **P* values comparing NHNT cohorts with versus without DM2 after propensity score matching (PSM). The T Test statistic compared the two cohorts after propensity matching to report differences between cohorts. *NS* non-significant *P* value, **p* value < 0.05. Mortality (degrees of freedom (df): 401, *P* = 0.182), hospitalization (df: 691, *P* = 0.09), ICU (df: 302, *P* = 0.127), stroke (df:112, *P* = 0.08), and cognitive dysfunction (df: 123, *P* = 0.01)

[OR 1.4; 95% CI (0.9–2.1); *P* = 0.08] after acquiring cryptococcosis when compared to NHNT patients without DM2 (Fig. 1).

Clinical Description of Patients Diagnosed with Cryptococcosis Following a Diagnosis of DM2 as the Only Risk Factor

We identified 44 patients with cryptococcosis who had DM2 as the only known risk factor for infection (Table 1). Other common comorbidities in this cohort included hyperlipidemia, hypertensive disease, obesity, ischemic heart disease, and CKD. A quarter of patients had hyperglycemia. The most common type of cryptococcosis was pulmonary (50%), followed by disseminated disease (36.4%) (Table 2). No patients were diagnosed with osseous or cutaneous forms of the disease. The mean hemoglobin A1c was 6.6.

Incidence and Prevalence of Cryptococcosis in Patients with DM2 as the Only Risk Factor

Of 2,657,812 patients living with DM2 without additional risk factors in the TriNetX system, the annual incidence of cryptococcosis was 0.001%, while the prevalence was 0.002%. The incidence and prevalence were similar among males and females. There was a higher prevalence of cryptococcosis among patients who identified as Black or African American (0.005%) or Hispanic or Latino (0.012%) compared to those who identified as White (0.002%).

Discussion

In this study, NHNT individuals with DM2 as a risk factor for cryptococcosis had increased cognitive dysfunction rates but not stroke compared to NHNT patients without DM2 in the year following the infection. There was no statistically significant difference in mortality, hospitalization, or ICU admission outcomes following a cryptococcal infection. An Argentinian-based study found increased mortality in cryptococcal meningitis patients with AIDS and diabetes (85.7% vs. 21.4%) [16]. Diabetic patients may have an impairment in cell-mediated immunity related to altered function of $CD8^+$ T-cells and natural killer cells [17]. Decreased macrophage and cytokine function (such as interleukin-12) may also play a role [18, 19]. Studies have shown an increased risk of multi-organ injury and death in diabetic patients with invasive infections [20]. In contrast to our results, previous studies with smaller cohorts have identified diabetes as a predictor of mortality for cryptococcosis [21, 22]. A case–control study in Taiwan found HIV-negative patients with cryptococcosis were more likely to have diabetes (OR 1.5), and the presence of diabetes was associated with an increase in 1-year mortality from cryptococcosis [23]. Diabetes is highly linked to glucocorticoid administration, which can worsen outcomes among invasive fungal infections and may have confounded previous findings. Cryptococcosis, especially meningitis, can lead to disabling sequela. Cryptococcus meningitis infection-mediated lacunar strokes—present in up to 26% of cases—can be responsible for cognitive impairment, speech difficulties, and gait imbalance [6, 24]. Our analysis shows that DM2 may contribute to cognitive impairment in patients with severe cryptococcal infection.

In the absence of known immunosuppressing conditions, such as HIV or being a transplant recipient, the development of cryptococcosis in patients with DM2 is rare. We found only 44 patients with cryptococcosis who had DM2 as their only risk factor for infection. These patients presented with pulmonary involvement and commonly had chronic kidney disease with ESRD. Immune dysfunction related to uremia and hyperglycemia can significantly impact cell-mediated immunity, increasing the risk for opportunistic fungal infections [25]. Reports have shown impairments in cell-mediated immunity in chronic kidney disease [26], including decreased $CD4^+$ and $CD8^+$ cell lines [27] and T-cell proliferation [28]. Although infrequent, renal failure with elevated creatinine can be comorbidity in patients with cryptococcal meningitis [24, 29]. To our knowledge, this is the first published large case series on patients with DM2 as their primary risk factor for cryptococcosis.

In this study, the annual incidence of cryptococcosis in patients with DM2 as their only risk factor was only 0.001%, and the prevalence was 0.002%. It can be challenging for providers to recognize cryptococcosis when it does occur in individuals without any identified immune deficiency. Based on our findings, cryptococcosis in patients with DM2 as the only risk factor was slightly more common among persons who identified as Hispanic, Latino, Black, or African American. A hospital-based calculation of cryptococcosis among patients with DM2 in China found a prevalence rate of 0.21% [7]. The higher rate in that study might have reflected a population with additional risk factors, including only hospitalized patients.

Pulmonary cryptococcosis was this study's most common anatomic site of cryptococcal infection for patients with DM2. A prior review of case reports of cryptococcosis in diabetic patients found higher rates of meningitis [7], perhaps due to additional immune compromise.

Limitations of this study included its retrospective design and constraints inherent in the TriNetX database. The retrospective nature of the study can allow for selection bias. Some cryptococcosis diagnoses by ICD codes can be subject to coding errors and the capture or exclusion of patients with errors in ICD codes. It is possible that cases of cryptococcosis identified by PCR were false positives, though these represented a small portion of identified cryptococcosis cases. We did not have access to culture data to confirm the cases clinically or differentiate between *Cryptococcus* species. Missing data can impair the strength of associations. ICD-10 coding cannot discriminate by type of stroke, as lacunar or basilar strokes are more specifically associated with cryptococcal meningitis. The TrinetX platform did not allow us to run subgroup analyses by participating centers. Patients in the NHNT cohorts had comorbidities that could confound findings, such as glucocorticoid use, cirrhosis, and chronic kidney disease. All patients with DM2 were analyzed as a single group, and the next step in this work could be to analyze subgroups based on how well the DM2 was controlled.

Conclusion

DM2 was associated with worse outcomes in patients with cryptococcosis, leading to increased cognitive dysfunction. It is rare for patients with DM2 to develop cryptococcosis as their only identified risk factor. Kidney disease, hyperglycemia, and immune dysfunction can increase risk in this setting. DM2 should not be listed as a primary risk factor for cryptococcosis without additional validation of the risk factor association.

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Author Contributions VMK contributed toward conceptualization; data curation; formal analysis; investigation; methodology; project administration; validation; writing—original draft; and writing—review and editing. CF contributed toward data curation; formal analysis; investigation; methodology; validation; writing—original draft; and writing—review and editing. MK contributed toward writing—review and editing. CF-P contributed toward conceptualization; and writing—review and editing. JT contributed toward writing—review and editing. LVB contributed toward writing—review and editing. LS contributed toward writing—review and editing. GRTIII contributed toward writing—review and editing. DBC contributed toward conceptualization; and writing—review and editing. AFH-M contributed toward conceptualization; data curation; formal analysis; investigation; methodology; project administration; software; supervision; validation; visualization; writing—original draft; and writing—review and editing.

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Data Availability The corresponding author had full access to data in the study and had final responsibility for the decision to submit the manuscript for publication. The datasets generated and analyzed in this study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr Shapiro reports receiving grants from the Emily Foundation for Medical Research during the study. Dr Henao-Martínez reported receiving a K12-clinical trial award as a co-principal investigator for the Expanded Access IND Program (EAP) to provide the Yellow Fever vaccine (Stamaril) to persons in the United States outside the submitted work. No other disclosures were reported.

Ethical Approval and Consent to Participate Research utilizing TriNetX does not require ethical approval because patient-identifiable informa-

tion is not accessible to users. The current project is in Health Insurance Portability and Accountability Act (HIPAA) compliance according to the Colorado Multiple Institutional Review Board (COMIRB) at the University of Colorado Denver. Analysis of clinical data was performed under an approved protocol.

Consent for Publication Not applicable.

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