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Brief Communication

SARS-CoV-2 and influenza co-infection: A cross-sectional study in central Missouri during the 2021–2022 influenza season

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ABSTRACT

As SARS-CoV-2 and influenza viruses co-circulate, co-infections with these viruses generate an increasing concern to public health. To evaluate the prevalence and clinical impacts of SARS-CoV-2 and influenza A virus co-infections during the 2021–2022 influenza season, SARS-CoV-2-positive samples from 462 individuals were collected from October 2021 to January 2022. Of these individuals, 152 tested positive for influenza, and the monthly co-infection rate ranged from 7.1% to 48%. Compared to the Delta variant, individuals infected with Omicron were less likely to be co-infected and hospitalized, and individuals who received influenza vaccines were less likely to become co-infected. Three individuals had two samples collected on different dates, and all three developed a co-infection after their initial SARS-CoV-2 infection. This study demonstrates high prevalence of co-infections in central Missouri during the 2021–2022 influenza season, differences in co-infection prevalence between the Delta and the Omicron waves, and the importance of influenza vaccinations against co-infections.

1. Introduction

Since the emergence of the coronavirus disease (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), more than 536 million confirmed cases and 6.31 million deaths have been reported worldwide (WHO Coronavirus) as of June 20, 2022. Prior studies suggest that among hospitalized patients with COVID-19 infections, co-infection with other respiratory viruses may be associated with more severe clinical outcomes and increased mortality (Swets et al., 2022). During the three influenza seasons overlapping the COVID-19 pandemic, co-infections of COVID-19 and influenza have been reported in multiple studies, with prevalence ranging from 0.2 to 45.7% (Dadashi et al., 2021; Stowe et al., 2021; Kim et al., 2020). However, the implications of co-infections in the general population, particularly during the most recent influenza season, remain unclear. To evaluate the prevalence and clinical impacts of SARS-CoV-2 and influenza A virus (IAV) co-infections, we performed a cross-sectional study in central Missouri during the 2021–2022 influenza season and investigated the associations of the latest COVID-19 variants of concern (VOC) with co-infections and clinical outcomes. Additionally, we assessed the association of COVID-19 and influenza vaccines with co-infection.

2. Materials and methods

Clinical swabs. Between October 1, 2021 and January 27, 2022, 466 SARS-CoV-2-positive nasal swab samples were collected from

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University of Missouri (MU) Health Care (including outpatient, inpatient, urgent care, and emergency department settings), and SARS-CoV-2 diagnosis was performed by the MU Microbiology and Molecular Laboratories. These swabs represented 462 individuals. Three individuals were associated with two swabs collected from different dates, and one individual with two swabs from the same date. For these four individuals, if one or both swabs tested influenza positive, this individual was considered as a single coinfection case.

Clinical data. Clinical data, which included demographic information, comorbidities, and influenza and COVID-19 vaccination history between 2020 and 2022, were also acquired from electronic medical records. Comorbidities and symptoms were collected using a combination of International Classification of Diseases (ICD)-10 codes along with review of physician free-text notes to ensure that all reported comorbidities and symptoms were captured. Symptoms were categorized by system as respiratory, gastrointestinal, cardiac, or constitutional and entered in the model as binary variables (present or not present). Individuals who received two doses of COVID-19 mRNA vaccines (i.e. Pfizer-BioNTech or Moderna) or one dose of the Janssen COVID-19 Ad26.COV2.S vaccine between 2020 and 2022 no less than three weeks prior to the date of swab collection were considered fully COVID-19 vaccinated. Individuals who received one dose of the COVID-19 Pfizer-BioNTech or Moderna mRNA vaccines at least three weeks prior to swab collection were considered partially vaccinated against COVID-19.

It has been well-documented that vaccine history affects host responses and outcomes against influenza ((Ohmit et al., 2014)(McLean et al., 2014; Ohmit et al., 2013; Poehling et al., 2018); ; ;). To account for both prior and current vaccinations, influenza vaccination history from the 2020–2021 and 2021–2022 seasons were included. Specifically, individuals who received an influenza vaccine between 2020 and 2022 no less than three weeks prior to the date of swab collection were considered influenza vaccinated.

Influenza testing and SARS-CoV-2 variant identification. Testing for IAV was performed using RT-qPCR targeting the IAV-M gene in triplicates, and a specimen was considered IAV-positive if the cycle threshold (Ct) $\leq$ 37.5 for all three replicates. The threshold was selected to detect 10 viral RNA copies per reaction. COVID-19 variants were identified using the VoXcreen-Delta-BA.1-2 qPCR assay (GenXpro) and/or whole-genome sequencing by MiSeq next-generation sequencing system (Illumina).

Statistical analyses. Logistic regression models (RStudio) were used to assess the association of the Omicron variant compared to the Delta variant and COVID-19 and influenza vaccinations with co-infection of SARS-CoV-2 and IAV. Additionally, logistic regressions were used to evaluate the association between the Omicron variant compared to the Delta variant and co-infections compared to single infections with clinical outcomes (hospitalization and symptoms). All models were adjusted for demographics (age in years, sex) and comorbidities (obesity, hypertension, cardiovascular disease, chronic lung disease, and diabetes). Statistical significance was defined at $p < 0.05$.

2.1. Ethical approval

This study was approved by the MU Institutional Review Board (#2049364).

Table 1
Demographic characteristics of study participants.

	Total		Single Infection		Coinfection	
	Count	**Percentage**	**Count**	**Percentage**	**Count**	**Percentage**
Total	**462**	**100%**	**310**	**67%**	**152**	**33%**
Age group						
0-8	40	8.7%	23	7.4%	17	11%
9-17	28	6.1%	13	4.2%	15	10%
18-49	271	59%	190	61%	81	53%
50-64	69	15%	51	16%	18	12%
65+	54	12%	33	11%	21	14%
Race/Ethnicity*						
White	402	87%	267	86.1%	135	89%
Black or African American	43	9.3%	29	9.4%	14	9%
Hispanic	6	1.3%	4	1%	2	1%
Asian	6	1.3%	5	2%	1	1%
Native Hawaiian or Other Pacific Islander	2	0.43%	2	1%	0	0%
Other or Unknown	11	2.4%	8	3%	3	2%
Sex						
Male	221	48%	145	47%	76	50%
Female	241	52%	165	53%	76	50%
Comorbidities						
Obesity (N = 232)**	100	43%	66	41%	34	48%
Hypertension	67	15%	42	9.1%	25	5.4%
Cardiovascular disease	25	5.4%	13	2.8%	12	2.6%
Chronic lung disease	31	6.7%	20	4.3%	11	2.4%
Diabetes	29	6.3%	18	3.9%	11	2.4%
Outcomes						
Hospitalization	25	5.4%	11	3.5%	14	9.2%
Respiratory Symptoms	190	41%	129	41%	61	40%
Gastrointestinal Symptoms	64	14%	39	12%	25	16%
Cardiac Symptoms	19	4.1%	12	3.8%	7	4.6%
Constitutional Symptoms	161	35%	112	36%	49	32%
Month of Swab						
October 2021	104	23%	54	17%	50	33%
November 2021	80	17%	48	15%	32	21%
December 2021	151	33%	90	29%	61	40%
January 2022	127	27%	118	38%	9	5.9%

The total number of individuals included in this study was 462. *Individuals may have more than one race or ethnicity. **Body mass index was available for 232 of 462 individuals.

3. Results

Our study population of 462 individuals with a laboratory confirmed COVID-19 infection was representative of all age groups, including young children and adolescents as well as individuals above 65 years (Table 1). Variant identification was attempted in 438 of 462 samples: 237 were infected with the Delta variant (51%), 174 with the Omicron variant (38%), and 27 with a variant other than Delta and Omicron (5.8%) (Fig. 1A). Genomic analyses of 18 sequenced samples revealed that 11 belonged to Delta (Phylogenetic Assignment of Named Global Outbreak Lineages [PANGOLIN] AY.3, AY.39, AY.100, AY.103, B.1.617.2), 6 to Omicron (BA.1, BA.1.1, BA.1.15), and 1 to lineage B. During our study period, IAV cases were peaking, with a total of 12,033 laboratory-confirmed influenza cases in the state of Missouri and 4,367 in central Missouri as reported by the Missouri Department of Health and Senior Services (Influenza Data, 2022). To identify the prevalence of SARS-CoV-2 and IAV co-infections, all 462 SARS-CoV-2-positive samples underwent additional IAV testing; 152 IAV-positive cases were identified, resulting in a 33% co-infection rate in our study population (Fig. 1B). Co-infection in our samples peaked in October 2021 at 48% (50 of 104 cases) when the Delta variant predominated and reached the lowest point at 7.1% (9 of 127 cases) in January 2022 when the Omicron variant prevailed. When both variants were co-circulating in December 2021, the coinfection rate was 44% (34 of 77 cases) for the samples with Delta variant and 27% (15 of 55 cases) for the samples with Omicron variant.

Logistic regression analysis revealed that infection with the Omicron variant is less likely to result in hospitalization (adjusted odds ratio [aOR] = 0.20, 95% Confidence Interval [CI] = 0.05, 0.87) compared to the Delta variant (Fig. 2A) after adjusting for age, sex, COVID-19 or influenza vaccination, co-infection (COVID-19, influenza), and comorbidities (obesity, hypertension, cardiovascular disease, chronic lung disease, and diabetes mellitus). Co-infection in the study population was not associated with clinical outcomes (hospitalization, cardiac, respiratory, constitutional, or gastrointestinal symptoms, or number of symptoms) after adjusting for the above covariates (Fig. 2B). Finally, individuals who were infected with the Omicron variant (aOR = 0.29, 95% CI = 0.14, 0.58) compared to the Delta variant (Fig. 2C) and those who received at least one influenza vaccine during the 2020–2022 influenza seasons (aOR = 0.36, 95% CI = 0.16, 0.81) compared to no influenza vaccination were less likely to become co-infected with both IAV and SARS-CoV-2 (Fig. 2D).

Of interest, four individuals were associated with two samples (Table 2). Our results showed that each individual had one influenza-positive and one influenza-negative swab. We noted that Individual D (Table 2) received two swabs on the same day. We speculate that the first swab had low sampling quality and thus, the second swab was collected. The time gap between two swabs for the other three individuals ranged from 1 to 12 days; our results showed that these three individuals started with a SARS-CoV-2 infection, and then later developed an influenza infection. None of the four individuals were vaccinated against influenza at the time of their first sample, although individual B was considered influenza-vaccinated (at least three weeks prior to the swab date) during their second swab. Individual C was fully vaccinated against COVID-19 during both swabs. None were admitted to the hospital. Individual B experienced respiratory symptoms during their initial swab, and individuals C and D experienced respiratory, gastrointestinal, and constitutional symptoms. Individual A did not report any symptoms.

4. Discussion

Among our study population, the prevalence of influenza co-infection among individuals infected with SARS-CoV-2 was 33% between October 2021 and January 2022, which was considerably higher than most recent studies (Dadashi et al., 2021; Stowe et al., 2021; Kim et al., 2020). However, these previous studies were conducted in 2020 and did not account for differences between SARS-CoV-2 variants. An additional study by Swets et al. conducted between February 2020 and December 2021 found that 227 of 6,965 SARS-CoV-2-positive patients were also infected with influenza virus (Swets et al., 2022). It is plausible that low co-infection rates in previous reports were due to study periods during low influenza activity, as influenza activity was historically low during the 2020–2021 influenza season largely due to non-pharmaceutical interventions implemented for COVID-19 control (Olsen et al., 2021), or additional factors including differences in COVID-19 variant predominance during different phases of the pandemic. On the other hand, it is also likely that the prevalence of co-infection has been underreported due to the diagnostic focus on COVID-19 during the pandemic. Individuals who are asymptomatic, not hospitalized, and

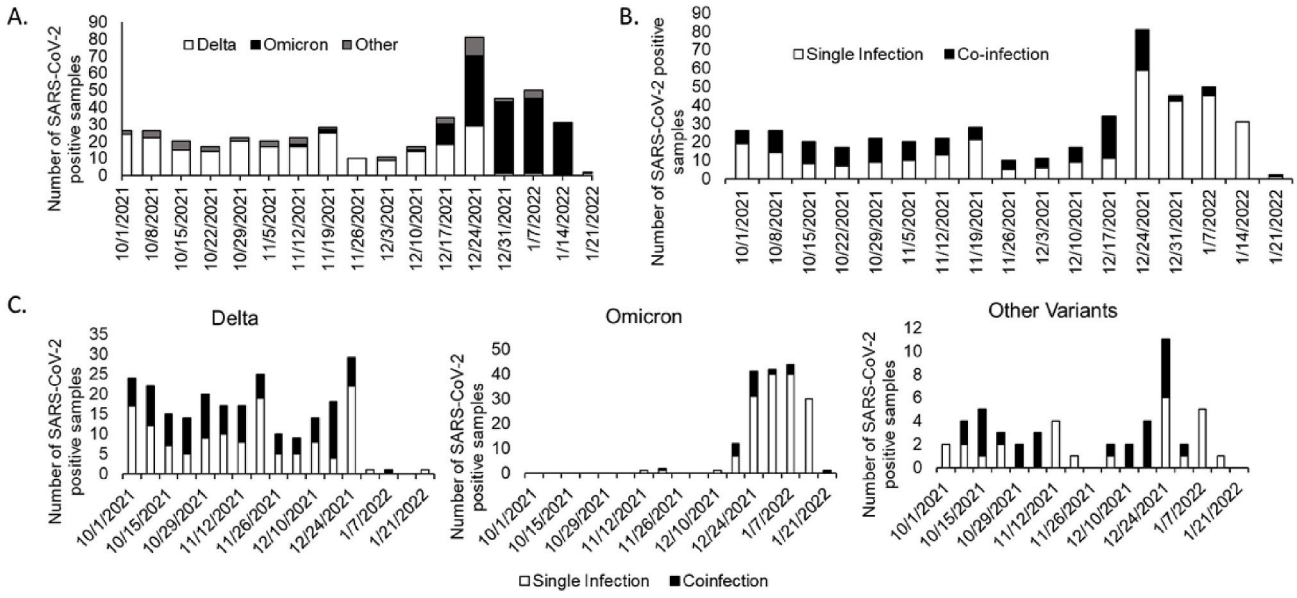

Fig. 1. Coinfection of SARS-CoV-2 and influenza A viruses in central Missouri during the 2021-2022 influenza season. A) Weekly occurrence of SARS-CoV-2 variants detected in central Missouri; B) Weekly occurrence of co-infection; C) Weekly occurrence of co-infection with Delta, Omicron, and other SARS-CoV-2 variants.

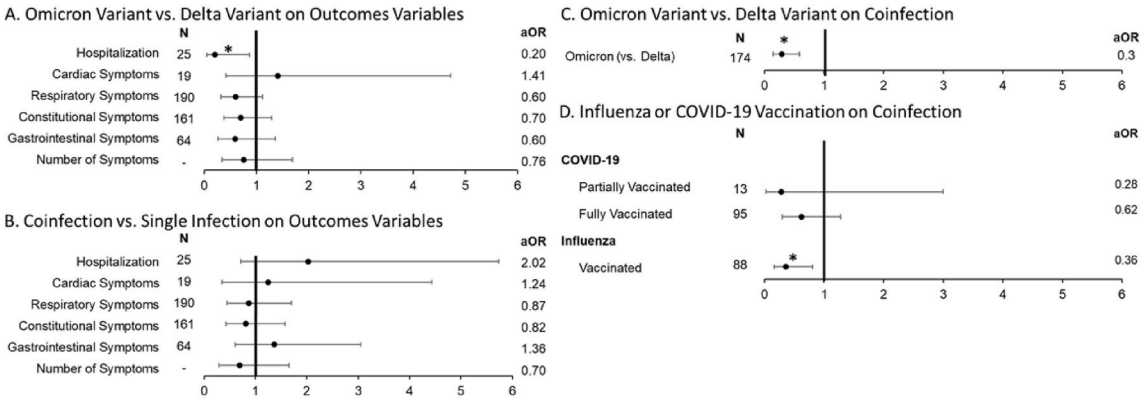

Fig. 2. Clinical impacts of SARS-CoV-2 and influenza A virus co-infections. A) Association of the Omicron variant compared to the Delta variant with hospitalization and symptom outcome variables; B) Association of coinfection compared to single infection with hospitalization and symptom outcome variables; C) Association of the Omicron variant compared to the Delta variant with coinfection as the outcome variable; D) Association of COVID-19 vaccination and/or influenza vaccination compared to no vaccination with coinfection as the outcome variable. Adjusted odds ratios (aOR) with 95% confidence intervals are shown. Number of symptoms were analyzed as a continuous outcome variable, whereas all other outcome variables were analyzed as presence or absence of the outcome (i.e., hospitalized vs. not hospitalized; cardiac symptoms vs. no cardiac symptoms); *, P-value < 0.05; All models in 2A-C were adjusted for age, sex, influenza vaccination (2020–2022), COVID-19 vaccination, coinfection, SARS-CoV-2 variant, and comorbidities (obesity, hypertension, cardiovascular disease, chronic lung disease, and diabetes mellitus). For coinfection models studying the association of vaccinations (2D), COVID-19 and influenza vaccinations were analyzed separately to avoid collinearity. All other variant, demographic, and comorbidity variables were included in the analyses. 95% confidence intervals that do not overlap with the value of 1 was considered statistically significant.

Table 2
Individuals with more than associated one swab sample.

Individual	Swab Date	Co-infection[a]
A	12/1/2021	No
A	12/13/2021	Yes
B	12/17/2021	No
B	12/23/2021	Yes
C	10/29/2021	No
C	10/30/2021	Yes
D	10/20/2021	No
D	10/20/2021	Yes

[a] The threshold for co-infection was influenza A virus cycle threshold (Ct) $\leq$ 37.5 for all three replicates.

have mild symptoms are typically not tested for influenza virus (Uyeki et al., 2019), and with the co-circulation of SARS-CoV-2 in recent years, many healthcare providers are testing for COVID-19 in individuals experiencing respiratory symptoms without additionally testing for influenza. Further, the Missouri Department of Health and Senior Services (Influenza Data, 2022) includes rapid influenza diagnostic tests (antigen), RT-PCR, and other molecular assays, immunofluorescence antibody staining, or viral culture for influenza testing. However, rapid influenza diagnostic tests and immunofluorescence assays, which are recommended for outpatient testing, have low to moderate sensitivity leading to higher false negatives compared with other molecular or RT-PCR tests. RT-PCR and other more sensitive molecular assays are only recommended for hospitalized patients (Uyeki et al., 2019). In this study, we applied RT-PCR in our analyses for all samples collected during the influenza peaking period, and this may explain why more SARS-CoV-2 and influenza co-infections were detected than previously reported. Nevertheless, we confirmed the presence of both subtype H3N2 and SARS-CoV-2 viruses in a subset of the samples through genomic sequencing.

Since the initial COVID-19 outbreak, an abundance of SARS-CoV-2 variants have emerged worldwide. The Delta variant of SARS-CoV-2 was first identified in late 2020 and became predominant until a new VOC, Omicron, emerged in November 2021 and rapidly spread to outcompete the Delta VOC (Jung et al., 2022). During the later pandemic phases, the emerging variants, particularly Omicron, showed distinct phenotypes from earlier variants. A recent study showed that, similar to human IAV (Shinya et al., 2006), Omicron (but not Delta) variant viruses primarily cause infections in the human upper respiratory tract because, in contrast to the Delta variant, Omicron has shifted towards human transmembrane serine protease 2 (TMPRSS2)-independent cell entry which favors infection of the upper respiratory tract (Zhao et al., 2022). During the 2021–2022 influenza season, our study showed that the Omicron variant was associated with fewer hospital admissions than the Delta variant (Fig. 2A). Of interest, our study suggested that co-infection of influenza with the Omicron variant may have been reduced compared to co-infection with the Delta variant (Fig. 1C), and further studies are needed to evaluate whether the Omicron variant is more likely than the Delta variant to act as an antagonist against IAVs, resulting in a lower co-infection risk.

Both SARS-CoV-2 and influenza are expected to cause recurrent epidemics and are very likely to co-circulate. Thus, co-infections may become more common in the coming years. Recent studies have reported that respiratory virus co-infections such as influenza and SARS-CoV-2 are associated with more severe clinical outcomes compared to single infections in hospitalized human studies (Swets et al., 2022; Stowe et al., 2021) and animal studies (Achdout et al., 2021; Kim et al., 2022; Kinoshita et al., 2021). Our study of individuals with SARS-CoV-2 infection showed that co-infection was not associated with more severe clinical outcomes. This may be due to our inclusion of non-hospitalized patients, which was largely comprised of individuals with mild or moderate symptoms compared to earlier studies of exclusively hospitalized patients (Swets et al., 2022; Stowe et al., 2021). Similar to our study, a meta-analysis by Guan et al. studying prior articles published before July 2021 found no overall increase in mortality or critical outcomes due to co-infections (Guan et al., 2021) and an additional study by Pawlowski et al. found no noticeable differences in hospitalization, intensive care unit admission, or mortality, although coinfection cases had reported more symptoms (Pawlowski et al., 2022).

In this study, we identified three individuals with two samples on separate days, and all three appeared to acquire influenza after a COVID-19 infection. As a future study, it will be interesting to investigate how likely it is for an individual to contract COVID-19 after an influenza infection or become infected with both influenza and COVID simultaneously. Additional studies are also needed to understand the dynamics of virus and host responses during co-infections.

As new COVID-19 variants continue to emerge, the clinical outcomes

of co-infections cannot be predicted and may potentially become more pronounced. Thus, testing for both SARS-CoV-2 and influenza viruses in individuals experiencing influenza-like illness should be encouraged, especially in people with increased risks of complications, as a prompt influenza and/or COVID-19 treatment can potentially help prevent more serious illness and/or hospital admission.

Finally, our results indicate that individuals who received at least one influenza vaccine during the 2020–2022 influenza seasons were less likely to be co-infected with SARS-CoV-2 and IAV. Of interest, interim estimates for the 2021–2022 seasonal influenza vaccine effectiveness report only 16% effectiveness against the A(H3N2) virus, although co-infections were not investigated in that report (Chung et al., 2022). Influenza vaccine effectiveness during the 2020–2021 season was not reported due to the historically low influenza activity (Olsen et al., 2021). Despite low vaccine effectiveness for the 2021–2022 season, our study highlights the importance of influenza vaccinations, as they appear to not only offer some protection against influenza infections but importantly, against SARS-CoV-2 and influenza co-infections.

Our study should be interpreted in consideration of its limitations. Our samples and data were collected from a single geographic area. Additionally, because the scope of our study investigates coinfections in the context of individuals with SARS-CoV-2, our samples were all SARS-CoV-2-positive. Thus, the prevalence of overall influenza and SARS-CoV-2 co-infections and the effectiveness of both COVID-19 and influenza vaccinations against co-infections remain unclear. Finally, there is a potential risk of selection bias. Because these swabs were collected from individuals who presented to the healthcare clinic, individuals who were more symptomatic were more likely to seek care and testing than those who were asymptomatic. Future studies involving multi-institutional and COVID-19-negative sampling will be necessary to address these remaining questions. Overall, testing for both influenza and SARS-CoV-2 viruses in individuals experiencing symptoms of respiratory illness and vaccinations against influenza and SARS-CoV-2 for all eligible individuals should continue to be encouraged.

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CRediT authorship contribution statement

Cynthia Y. Tang: Data curation, Methodology, Software, Investigation, Writing – original draft, Writing – review & editing, Visualization, Project administration, Funding acquisition. **Maria Boftsi:** Data curation, Methodology, Investigation, Writing – original draft. **Lindsay Staudt:** Data curation, Writing – review & editing. **Jane A. McElroy:** Writing – review & editing, Supervision, Project administration. **Tao Li:** Data curation, Writing – review & editing. **Sabrina Duong:** Data curation, Writing – review & editing. **Adrienne Ohler:** Methodology, Validation, Writing – review & editing, Supervision. **Detlef Ritter:** Resources, Writing – review & editing. **Richard Hammer:** Resources, Writing – review & editing. **Jun Hang:** Resources, Writing – review & editing. **Xiu-Feng Wan:** Conceptualization, Methodology, Investigation, Resources, Writing – original draft, Writing – review & editing, Supervision, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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