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Epidemiology of circulating influenza viruses in Ethiopia during the COVID-19 Pandemic: Evidence from National Severe Acute Respiratory Infection and Influenza-Like Illness Sentinel Surveillance (January 2021-August 2022)

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Influenza is an acute viral respiratory tract disease in humans, often characterized by fever, headache, myalgia, prostration, coryza, sore throat and cough. Influenza infection is clinically indistinguishable from other respiratory viral diseases without laboratory confirmation. This study aims to estimate the proportion of confirmed influenza cases among patients presenting with a severe acute respiratory infection (SARI) and influenza-like illness (ILI) to determine its epidemiological distribution and guide surveillance and public health interventions. This study was based on analysis of surveillance data from 19 of these health facilities, January 2021 to August 2022. Epidemiological and virologic data were collected from these facilities. laboratory testing was carried out at the Ethiopian Public Health Institute (EPHI). Multivariable logistic regression analysis was used to identify factors associated with the positivity of influenza tests, and results are expressed as adjusted odds ratios (AORs). Among the 6,193 patients included in this study, 11.1% tested positive for influenza. Higher influenza positivity was detected among ILI cases (26.4%, 525) compared to SARI cases (3.8%, 161). Peaks in influenza positivity occurred during February and December. The positivity of influenza tests was significantly associated with patients. The positivity rate for influenza virus during the study period was relatively high in Ethiopia. Strengthening laboratory capacity and influenza sentinel surveillance to detect influenza and other respiratory pathogens is recommended to allow public health officials to interpret national data, compare trends over time locally and globally, and to be prepared for future outbreaks.
Key words: Influenza, SARI, sentinel site, COVID 19, Ethiopia

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INTRODUCTION

Influenza is an acute viral respiratory tract disease in humans, often characterized by fever, headache, myalgia, prostration, coryza, sore throat, and cough. It is caused by the influenza virus, an RNA virus in the Orthomyxoviridae family, and is clinically indistinguishable from other respiratory viral diseases without laboratory

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confirmation (WHO, 2015). There are four types of influenza viruses: Influenza A, B, C, and D. Type A is capable of infecting multiple species, including birds; types B and C occur only in humans, and type D primarily affects livestock species (Uyeki 2022).

The World Health Organization (WHO) estimates that globally there are 3-5 million cases of severe illness and 290,000-650,000 deaths annually due to influenza-related respiratory diseases alone (Sambala et al., 2018). In tropical developing countries, the pattern of influenza circulation may differ markedly from that in temperate and developed settings. Influenza surveillance conducted in fifteen countries in Africa from 2006 to 2010 showed that children aged 0–4 years accounted for 48% of all cases of influenza-like illness (ILI) and severe acute respiratory infection (SARI). Twenty-two percent of ILI and 10% of SARI patients tested positive for influenza virus. Seasonal influenza typically occurs every year in late fall or winter in temperate regions, while its seasonality is less clearly defined in tropical and subtropical regions (WHO, 2019).

Different studies from high-income countries have identified various subtypes of influenza and described their epidemiological, clinical, and seasonal characteristics (Mosnier et al., 2015). However, the epidemiology of ILI and SARI is not well understood in low- and middle-income countries (LMICs) like Ethiopia. Only a few studies of seasonal influenza outbreaks in Africa have reported high case fatality associated with the disease (Mosnier et al., 2015). Moreover, a limited number of studies in Africa have identified variants of influenza circulating in their countries. For instance, a study conducted in the Democratic Republic of Congo reported detection of influenza A virus (IAV) H3N2 and H1N1, and influenza B virus (IBV) (Umuhoza et al., 2020). In Ethiopia, data collected from the National Influenza Sentinel Surveillance System sites from 2009 to 2015 also reported circulation of IAV H3N2 and H1N1, and influenza B virus (Chow et al., 2019). However, these studies were limited by the inclusion of an inadequate number of SARI patients in their analysis and did not determine positivity rates in different population groups. Moreover, lessons learned from the COVID-19 pandemic underscore the importance of continuous surveillance, detection, and identification of influenza virus strains circulating in the country to prevent and control potential outbreaks. Ethiopia has been implementing SARI and ILI sentinel surveillance since 2008 (Ayele et al., 2012) with the aim of detecting any new influenza strains with specific characteristics and determining the proportion of confirmed influenza cases among SARI in hospitalized inpatients and/or among ILI in community outpatients. This study aims to estimate the proportion of confirmed influenza cases among SARI/ILI patients, determine its epidemiological distribution, and identify associated risk factors to guide surveillance and public health interventions in Ethiopia.

MATERIALS AND METHODS

Study setting and source of data

This study was based on the analysis of data collected from the Ethiopian National Influenza Sentinel Surveillance System. The National Influenza Sentinel Surveillance System of Ethiopia is currently implemented in 20 selected healthcare facilities (16 SARI hospitals and four ILI health centers) across eight regions and two city administrations as shown in figure 1. Selection of the health facilities was guided by WHO standards (WHO, 2015). This study included data captured from 19 health facilities, as one of the health facilities in the Northern part of the country did not collect any samples during the study period due to security issues in the region. ILI health centers are only located within the Addis Ababa city limits.

Study design

A retrospective, cross-sectional study design was used to capture data from patients who visited the sentinel surveillance sites from January 01, 2021 through August 20, 2022.

Case definition of SARI and ILI

According to the WHO global epidemiological surveillance standards for influenza, ILI is defined as an acute respiratory illness (ARI) with a measured temperature of ≥38°C and cough, with onset within the last 10 days. SARI is defined as an ARI with a history of fever or measured fever of ≥38°C and cough, with onset within the last 10 days, and requiring hospitalization (WHO, 2016).

Case enrollment data collection procedures and specimen transportation

Standard WHO case definitions of SARI/ILI were used to enroll patients in a surveillance program during their visit to selected health facilities (WHO, 2015). Accordingly, ILI was identified among patients attending outpatient clinics, and SARI was identified among patients admitted to hospitals. Patients were sampled for laboratory testing, and epidemiological data were collected based on a sampling strategy to enroll ILI and SARI cases. For ILI case enrollment, among outpatients who met ILI case surveillance specimen transportation. Patients' socio-demographic information and epidemiological data were collected using a standard case system each day. Throat or nasopharyngeal specimens were collected if the patient presented within the first ten days after the onset of symptoms. Throat swab samples were placed in viral transport media (VTM) and stored at 4°C until transported to the National Influenza Center (NIC) at the Ethiopian Public Health Institute (EPHI), following a triple packaging system during reporting form. The reporting form, along with its complete recorded information and weekly aggregate of SARI/ILI cases containing the proportion of influenza, was submitted to EPHI.

Laboratory testing

Viral ribonucleic acid (RNA) was extracted from the swabs and subjected to reverse transcription- quantitative polymerase chain reaction (RT-qPCR) amplification with parameters set for influenza testing, according to the WHO protocol (WHO, 2016). All RT-qPCR runs were performed together with appropriate controls. The results were interpreted based on cycle threshold (Ct) values in reference to positive and negative controls. A Ct value of <37 was considered

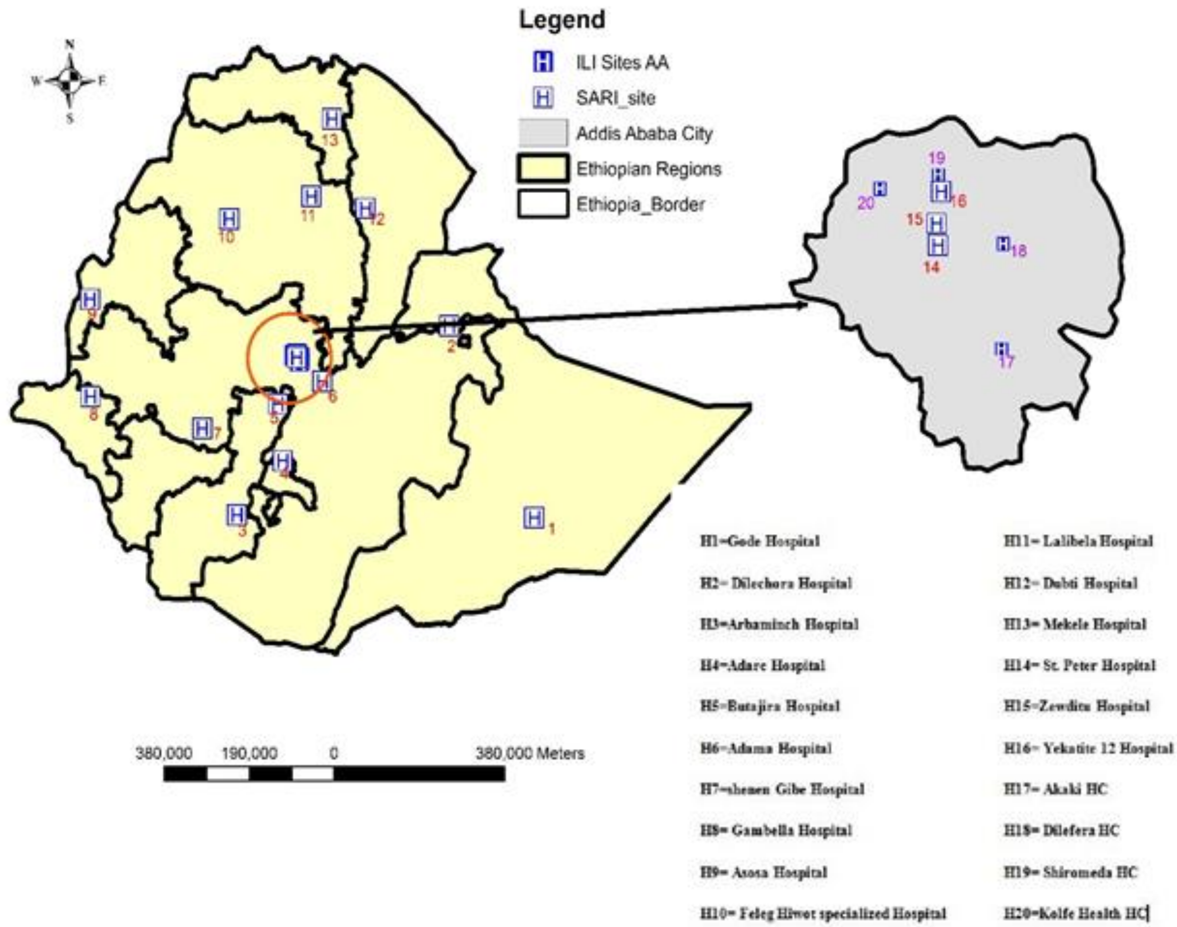

Figure 1. Map showing Influenza sentinel sites in Ethiopia, 2022 [ILI sites are only in Addis Ababa]. H: health facility for SARI case enrollment; HC: health center for ILI case enrollment.

positive, and those values ≥ 37 were deemed as negative. Samples that tested positive for IAV were further subtyped using subtype-specific oligonucleotide primers (Wang et al., 2013). The epidemiological data and laboratory results were linked using unique identifiers and the results were completed at National Influenza Center (NIC) EPHI.

Statistical analysis

SARI/ILI data reported to the EPHI database from the sentinel sites were retrieved and cleaned in Microsoft Excel, then exported to Stata for analysis (StataCorp. 2021. Stata Statistical Software Release 17. College Station, TX, StataCorp LLC). Descriptive statistics were conducted to determine the frequency and proportions of the categorical variables, as well as the means and standard deviations of the continuous variables. Factors associated with influenza virus positivity were identified first by bivariable logistic regression, followed by multivariable logistic regression analysis. Variables with p-values < 0.25 in the bivariable analysis were included as candidate variables for the multivariable analysis. Positivity for influenza was used as the outcome variable for the regression analysis, with explanatory variables including patient age, sex, specimen type, and region. Patients' ages were grouped based on the WHO age classification for influenza patients (WHO, 2016). The findings of the multivariable analysis were expressed as 95% confidence intervals (CIs) and adjusted odds ratios (AORs). The level of significance was set at 5%.

RESULTS

Demographic characteristics

This study analyzed data from 6,193 patients who fulfilled the ILI and SARI WHO case definitions. More than two-thirds (67.9%) of the participants were SARI inpatients and more than half (53.1%) were males (Table 1). The mean age of the study participants was 21.2 years (±22.6).

Influenza positivity by age group and region

Of the 6,193 patients evaluated for influenza, 686 were found to be influenza positive (11.1% (95% CI: 10.3 - 11.9) positivity rate). Confirmed influenza cases were

Table 1. Influenza positivity among SARI and ILI cases by age group, sex and specimen type, January 2021- August 2022.

Variable	Category	Total N=6193	ILI		SARI	
		N (%)	Total	No. Positive (%)	Total Test	No. Positive (%)
Age group	<2	1794 (29.0)	258	38 (14.7)	1536	67 (4.4)
	2-<5	705 (11.4)	227	46 (20.3)	477	26 (5.5)
	5-<15	641 (10.4)	310	110 (35.5)	331	13 (3.9)
	15-<50	2104 (34.0)	1056	313 (29.6)	1048	21 (2.0)
	50-<65	551 (8.9)	87	10 (11.5)	464	19 (4.1)
	65+	399 (6.4)	48	8 (16.7)	351	15 (4.3)
Sex	Female	2905 (46.9)	1070	273 (25.5)	1834	63 (3.4)
	Male	32809 (53.1)	916	252 (27.5)	2373	98 (4.1)
Specimen type	Throat swab	4141 (66.9)	1004	264(26.3)	3137	108 (3.4)
	NP swab	2052 (33.1%)	982	261 (26.6)	1070	53 (5.0)

ILI: Influenza like illness; SARI: severe acute respiratory infection; NP: nasopharyngeal.

highest among patients aged 5-15 years (19.2%) followed by 15-50 years (15.9%) and 2-5 years old (10.2%), respectively. Based on patient categories, a higher positivity rate was found in the ILI cases (26.4%) compared to the SARI cases (3.8%). Among regional states of the country, the Addis Ababa City Administration showed the highest influenza positivity rate (18.2%) followed by the Afar and Amhara regional states, which had positivity rates of 5.6 and 5.5%, respectively (Table 2). Of the total positive influenza cases, 62% were identified as IAV (61% AH3 and 1% AH1) and 38% were identified as IBV (Figure 2).

Influenza positivity by sentinel sites

The ILI sentinel sites with the highest influenza positivity rates were the Akaki Health Center, Dilfere Health Center, Kolfe Health Center and Shiromeda Health Center, with 17.2, 20.5, 22.1 and 34.7% positivity rates, respectively. The SARI sites with the highest influenza positivity rates were the Felege Hiwot Compressive Specialized Hospital in the Amhara region, St. Peter Specialized Hospital in Addis Ababa, Dubti Hospital in the Afar region, and Asosa Hospital in the Benishangul-Gumuz Region with 5.9, 5.7, 5.6, and 5.2% positivity, respectively (Table 2).

Influenza positivity among SARI and ILI cases by age group, gender, and specimen type

Influenza positivity was highest in the age group 5-15 years old 310 (35%) among ILI cases and 2-5 years old age group 26 (5%) among SARI cases (Table 1).

Influenza seasonal trend

Greatest peaks in influenza positivity rate were seen between February and March and between November and December of 2021 (Figure 3). A smaller peak was again observed between February and March of 2022, with a slightly larger peak occurring between May and July of the same year.

Factors associated with influenza positivity rate

In the multivariable analysis (Table 3), the influenza virus positivity rate was significantly associated with age, specimen type and region, whereas it was not associated with the sex of the patient. The odds of influenza virus positivity were 1.61, 3.01, and 2.74 times higher among patients in age groups 2-5, 5-15, and 15-50 years, respectively, compared to patients less than 2 years of age. Similarly, the odds of influenza virus positivity were 1.5 times higher among those patients whose samples were taken from the nasopharynx as compared to samples taken from the throat. Regionally, the odds of influenza virus positivity were four times higher among patients in Addis Ababa as compared to patients reported from outside of Addis Ababa.

Ethics consideration

This surveillance system is considered to be a routine surveillance led by the Ethiopian Public Health Institute, as the agency has the legal mandate to conduct surveillance for the early identification and detection of public health risks and prevent public health emergencies. In addition, the surveillance and the data analysis under

Table 2. Total number of specimen and proportion of influenza positivity by, SARI and ILI Sentinel sites in Ethiopia, January 2021- August 2022.

Region	Total	Influenza positive n (%)	Sentinel Sites	Site Category	Catchment population	Total Test	#Influenza positive	Positivity rate (%)	Cases per 100,000
Addis Ababa	3133	571 (18.2)	Akaki HC	ILI	36,120	542	93	17.2	257.5
			Dilfire HC	ILI	52,117	215	44	20.5	84.4
			Kolfe HC	ILI	72,342	429	95	22.1	131.3
			Shiromeda HC	ILI	39,176	847	294	34.7	750.5
			St. Peter S. Hospital	SARI		331	19	5.70	
			Yekatit 12 Hospital	SARI		513	13	2.50	
			Zewditu S. Hospital	SARI		298	13	4.40	
Afar	408	23 (5.6)	Dubti Hospital	SARI	1,000,000	408	23	5.60	2.3
Amhara	255	14 (5.5)	Felege Hiwot CSH	SARI	10,000,000	236	14	5.90	0.1
			Lalibela Hospital	SARI		17	0	0.00	
Benishangul Gumuz	230	12 (5.2)	Asosa Hospital	SARI	477,625	230	12	5.20	2.5
Dire Dawa	536	20 (3.7)	Dilchora Hospital	SARI	1,500,000	571	20	3.50	1.3
Gambella	29	0	Gambella Hospital	SARI	65,395	29	0	0.00	0
Oromia	440	10 (2.3)	Adama CST Hospital	SARI	6,000,000	194	4	2.10	0.1
			Shanan Gibe Hospital	SARI	1,500,000	176	6	3.40	0.4
Sidama	439	22 (5.0)	Adare Hospital	SARI	1,400,000	476	22	4.60	1.6
SNNPR	519	12 (2.3)	Arbaminch Hospital	SARI	4,200,000	372	8	2.20	0.2
			Butajira Hospital	SARI	1,500,000	109	4	3.70	0
Somali	204	2 (1.0)	Gode Hospital	SARI	1,500,000	200	2	1.00	0.1
Total	6193	686 (11.1)				6193	686	11.10	

ILI: Influenza-like illnesses; SARI: severe acute respiratory infection; SNNPR: Southern Nations, nationalities and peoples region.

this manuscript is guided by a national Influenza Sentinel surveillance protocol, approved by the Ethiopian Public Health Institute director. Moreover, the surveillance has received a non-research determination from US-Center for Disease Control and Prevention (US-CDC).

DISCUSSION

This study sought to analyze influenza sentinel surveillance data captured from 19 health facilities from January 2021 to August 2022 to provide a proportion of confirmed influenza cases by type and determine the epidemiological distribution of the virus among sentinel sites. Influenza was widespread in established Ethiopian sentinel surveillance sites where patients were enrolled. Despite differences in population distribution and topography, influenza viruses (influenza AH1 and

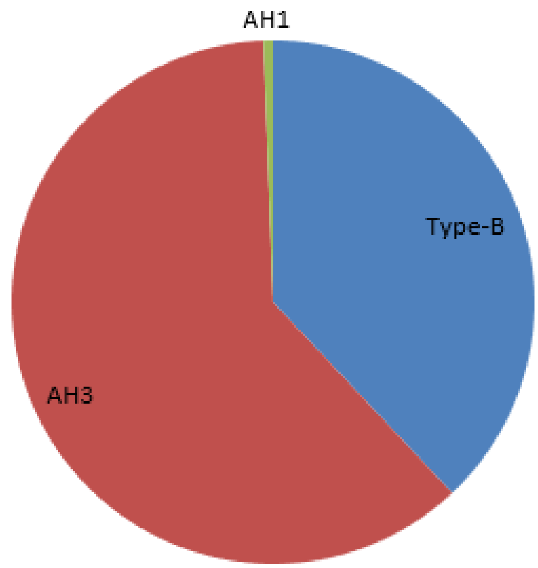

Figure 2. Type and sub-type of circulating influenza virus in Ethiopia, Severe Acute Respiratory Infection (SARI)/Influenza - Like Illness (ILI) Sentinel Surveillance, January 2021- August 2022.

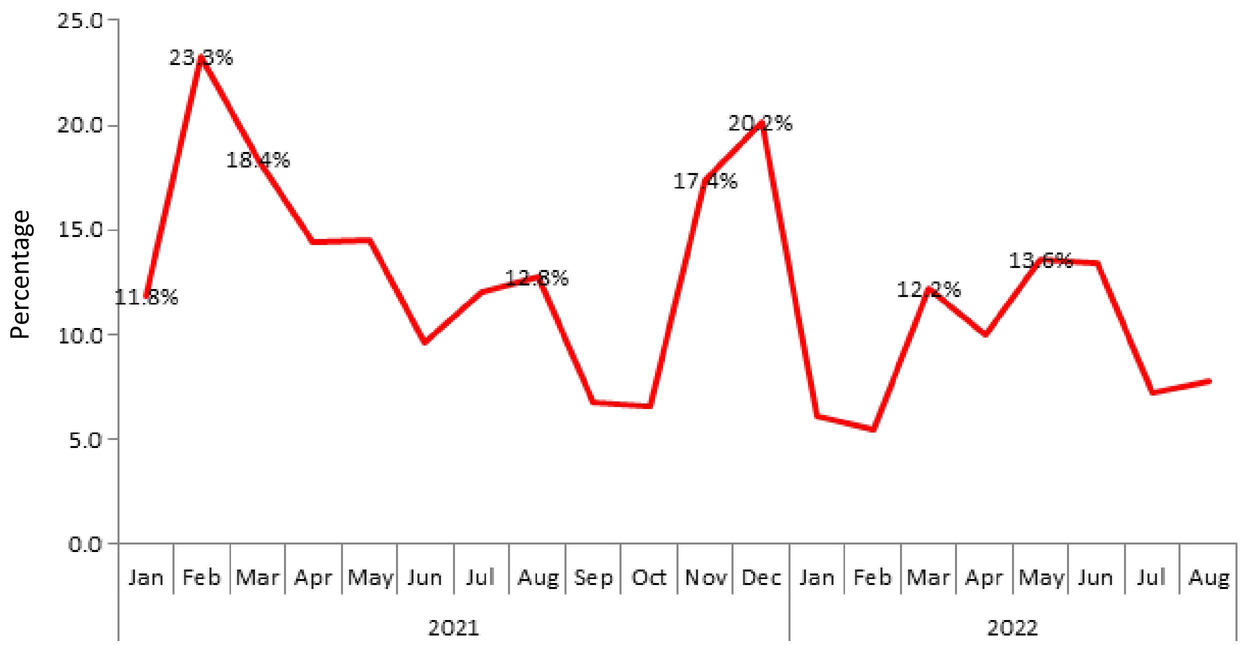

Figure 3. Trend of proportions of influenza virus positive cases by month, Severe Acute Respiratory Infection (SARI)/Influenza - Like Illness (ILI) Sentinel Surveillance in Ethiopia, January 2021- August 2022.

AH3 and influenza B) were found in all of the study areas (Manirakiza et al., 2017; Care et al., 2022; Uyeki et al., 2019). The overall influenza positivity rate was 11.1% consisting of predominantly IAV H3 followed by IBV. Moreover, this study also showed the variation of influenza positivity by specimen type, age category and regional states. A higher positivity rate was recorded from nasopharyngeal compared to throat swabs, age group between 5 to 15, and Addis Ababa administrative city.

Although it has been reported by several previous studies that influenza peaks during winter seasons in the temperate regions and is invariable in the tropical regions

Table 3. Results of logistic regression model for factors associated with influenza positivity, severe acute respiratory infection (SARI)/influenza - like illness (ILI) sentinel surveillance in Ethiopia, January 2021-August 2022.

Variable	Crude Odds ratio		Adjusted Odds Ratio			
	OR	p-value	AOR	S.E	p-value	AOR-95% CI
Sex of patient						
Male	Ref.					
Female	1.09	0.245	0.89	0.0816	0.226	[0.7488, 1.0707]
Age category						
Less than 2	Ref.					
2 -< 5	1.83	0.000*	1.61	0.2689	0.004*	[1.1612, 2.2343]
5 -< 15	3.82	0.000*	3.01	0.4680	0.000*	[2.2226, 4.0857]
15 -< 50	3.04	0.000*	2.74	0.3420	0.000*	[2.1419, 3.4959]
50 -< 65	0.89	0.602	1.32	0.2971	0.221	[0.8473, 2.0500]
65 and above	0.98	0.628	1.42	0.3523	0.158	[0.8728, 2.3089]
Specimen type						
Throat swab	Ref.					
Nasopharyngeal swab	1.83	0.000*	1.53	0.1408	0.000*	[1.2795, 1.8345]
Region						
Other regions	Ref.					
Addis Ababa	5.71	0.000*	4.74	0.5236	0.000*	[3.8199, 5.8884]

OR: Crude odds ratio; AOR: Adjusted Odds Ratio; SE: Standard error; 95%CI= 95% Confidence Interval; *Significant at 5%.

(Tamerius et al., 2013; Finkelman et al., 2007; Dave and Lee, 2019), this study finding revealed that it peaks during the dry seasons of the year (November – December and February – March). This finding of the study implies that the nature of the virus and environmental (climate) conditions might play key roles in the survival and transmission pattern of the virus. Currently, the global climate change is affecting the humidity, temperature, precipitation, and the rainfall distribution, varying trends may be observed from what is expected. Thus, it is important to continuously monitor and record the local climate conditions rather than simply labeling the geographic regions as temperate or tropical to differentiate and trend over time the actual seasonality of the influenza infection. Therefore, ascertainment of the seasonality of the influenza infection requires robust capture of climatic data and analysis of the longer-term surveillance data.

In line with findings from studies conducted in various African countries (Miring'u et al., 2022; Soudani et al., 2022; Gomaa et al., 2022), the positivity rate of influenza virus among laboratory samples from ILI/SARI patients was significant. The proportion of laboratory-confirmed influenza in this study was higher (11.1%) compared to reports from Nigeria (7.7%) (Dalhatu et al., 2012) and the Central African Republic (8.4%) (Manirakiza et al., 2017), but lower than a study in Kenya (19%) (Umuhoza et al., 2020). These differences may reflect disparities in laboratory methods, patient recruitment through surveillance systems, sample types, and collection times.

Furthermore, influenza positivity was found to be higher among ILI patients (26.4%) compared to SARI patients (3.8%) in this study, which aligns with findings in Morocco (34.6% ILI and 11.9% SARI) (Ezzine et al., 2020) and Bangladesh (10% ILI and 6% SARI) (Zaman et al., 2009). Variations in positivity rates between ILI and SARI patients could be attributed to differences in sample quality and timing of collection. SARI patients, often hospitalized and seriously ill, may find it challenging to provide high-quality samples. Conversely, the lower influenza positivity among SARI patients might suggest that many SARI cases are caused by pathogens other than influenza, as routine surveillance may not routinely screen for other respiratory pathogens among ILI and SARI patients.

In comparison to other regions of Ethiopia, Addis Ababa city exhibited a higher magnitude of influenza positivity. Addis Ababa serves as Ethiopia's capital and a hub for numerous national and international organizations, as well as international air travel. Additionally, residents of Addis Ababa have higher health literacy and better health-seeking behavior compared to those in other parts of the country (EPHI, 2019). Moreover, since all ILI surveillance sites are located in Addis Ababa, a higher incidence of influenza cases is expected in the city compared to other regions.

Age emerged as a significant factor associated with influenza positivity among patients. Consistent with findings from studies in Ethiopia (Woyessa et al., 2018), Cameroon (Njouom et al., 2019), Egypt (Gomaa et al., 2022), and Indonesia (Adisasmito et al., 2019), school-age children (5-15 years) were most affected by the influenza virus. Given that influenza spreads easily through air or droplets, school-age children spend their days in enclosed spaces with insufficient ventilation, making them particularly vulnerable. In contrast to this study, older patients were identified as high-risk for influenza infection in other research (Hardelid et al., 2017; Guesneau et al., 2021; Lee et al., 2021). Variations in reported positivity rates among age groups may stem from actual differences in influenza incidence across countries, variations in surveillance system quality, community health-seeking behavior, and differences in sentinel surveillance approaches.

Nasopharyngeal swab specimens were more predictive of influenza positivity rates compared to oropharyngeal swab samples. The observed differences in positivity rates by specimen type in this study have implications for future sample collection methods within Ethiopia's sentinel surveillance system. In routine clinical practice, the choice of sample collection method should consider feasibility, test reliability (sensitivity and specificity), sample adequacy, time requirements, and patient comfort and acceptance.

This study highlights that nasopharyngeal sampling is superior to oropharyngeal swabs in yielding influenza virus detection. This finding is supported by other studies indicating that oropharyngeal samples have lower sensitivity and poor positive predictive value, leading to reduced virus detection compared to nasopharyngeal specimens (Hernes et al., 2013; Heikkinen et al., 2002; Irving et al., 2012).

Although this study collected data from a large sample size obtained from nationally representative SARI/ILI sentinel sites and conducted testing at a well-monitored National Influenza Center, it is limited by the lack of data over a longer period to fully capture influenza seasonality. Additionally, the study did not incorporate regional climate data, which could have provided insights into the relationship between infections and specific climatic variables. Moreover, important factors such as comorbidities and vaccination status were not adequately captured through the surveillance system. Future investigations should consider these variables to enhance understanding of influenza virus infection positivity.

Conclusion

Ethiopia recorded significant proportions of influenza virus positivity, with peaks observed in February and December. Throughout the study period, influenza types AH1N1 and AH3N2 predominantly circulated across all regions of Ethiopia. The positivity rate for influenza among SARI and ILI patients varied by age group and specimen collection methods. A prospective study is needed to assess comorbidities as risk factors for influenza-associated SARI. It is crucial to strengthen laboratory capacity and enhance influenza sentinel surveillance to detect other respiratory pathogens. This approach is essential for public health to accurately interpret national data, monitor seasonal trends, and prepare for future outbreaks both locally and globally.

CONFLICT OF INTERESTS

The author has not declared any conflict of interests.

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