UNIVERSITY OF NAIROBI

HUMAN RESPIRATORY SYNCYTIAL VIRUS, HUMAN PARAINFLUENZA VIRUS AND HUMAN ADENOVIRUSES' EPIDEMIOLOGY, CLINICAL CHARACTERISTICS AND ASSOCIATED FACTORS IN KENYA: A RETROSPECTIVE INVESTIGATION 2007-2013

BY

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A thesis submitted in the fulfilment of the requirements for the Award of the Degree of the Doctor of Philosophy in Tropical and Infectious Diseases at the University of Nairobi

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DECLARATION

In a submission of this PhD thesis, I acknowledge that it is my original work. No part of this work has been submitted by myself, or by other persons to other institutions for other academic awards. THERESE UMUHOZA, BSc, MSc. Epidemiology (W80/52901/2018); the University of Nairobi, Institute of Tropical and Infectious Diseases; Email: umuhozateddy@gmail.com

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DEDICATION

To God who gives us life and health. To those who could not get their education due to any form of discrimination, whether based on race, gender or regions. To my loving family dearest!

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LIST OF OPERATIONAL DEFINITIONS

Aetiology: The study of a disease causation

Bias: Any systematic error that leads to inaccurate conclusions or results

Burden: The effect of a health problem in a given population

Confidence interval: It is a range of values where probabilities of specified parameters lie within the values range limit

Comorbidity: Simultaneous occurrence of diseases in an individual patient

Covariate: An independent variable that is measurable and considered to influence the outcome

Disability: Any medical condition that makes it difficult for a person to perform certain activities or interact effectively with the world around them

Data: Factual information gathered through observation

Dataset: A structured collection of data

Denominator: Values that are expressing the total population figure in statistical terms

Determinant: Any factor that can influence the prevalence of disease and distribution in a particular population

Epidemiology: The study of disease in populations and of factors that determine its occurrence

Epidemic: The occurrence of excessive cases of disease than expected in a given population or area during a particular period

Frequency: The number of times a repeating event occurs per unit of time.

Heterogeneity: Variations or differences in data of population, sample or outcome

Immunization: The action of making a person or animal immune to infections

Infection: The invasion of disease-causing pathogens in an organism's body or tissues

Incidence: The occurrence of a new disease in a population at a specific time

Incidence rate: The number of new cases per population at risk in a given time

Incubation period: The time between pathogen infection and the onset of illness or disease symptoms.

Likelihood ratio: The probability of a given infection in a patient versus the probability of a given infection not being in a patient

Magnitude: The property of larger or smaller size

Meta-analysis: A statistical method of analysis that combines the findings of several scientific studies.

Morbidity: Any departure, subjective or objective from a state of physiological and psychological well being

Mortality: The state of being subject to death

Numerator: Refer to the up number of the fraction

Occurrence: Frequency of a disease in a population

Outbreak: A sudden increase in the number of disease frequency in a place, time and population

Outlier: An observation that is abnormally distant from normal values

Phase: The steps in a series of disease occurrence events

Pneumonia: Inflammation of the lung

Prevalence: The proportion of a disease in a population at a given time

Proportion: The fraction of the total disease possession

Rate: The measure of the frequency of diseases

Ratio: The expressions for one measure in relation to another

Rhinorrhea: The excessive discharge of nasal mucus fluids.

Risk: The probability of an event to occur in a specified time

Sample: A set of observations delivered from a population

Sign: The observed evidence of a disease in an individual patient

Specimen: Refer to the biological part of an organism

Surveillance: The process of systematic monitoring, gathering, analyzing and interpreting information of occurring event

Study population: The population from which a sample is drawn

Symptom: The evidence of a disease provided by an individual patient

Syndrome: A set of symptoms that consistently occurring together

Systematic review: A repeatable analytical method for synthesizing evidence

Target population: The total population of which information is required

Variable: An observation that is likely to vary

LIST OF ABBREVIATIONS AND ACRONYMS

ARIs: Acute respiratory illnesses

ALRTIs: Acute lower respiratory tract infections

CDC: US centers for disease control and prevention

DEID: Department of Emerging Infectious Diseases

DNA: Deoxyribonucleic acid

ERD: Enhanced respiratory syncytial virus disease

HAdVs: Human adenoviruses

HMPVs: Human metapneumo-viruses

HPIVs: Human parainfluenza viruses

HRSV: Human respiratory syncytial virus

HSV1: Herpes simplex virus one

IHR: international health regulations

ILI: Influenza-like illness

ILRI: International livestock research institute

IRB: Institutional Review Board

KEMRI-SSC: Kenya medical research institute- scientific committee

LRTIs: Lower respiratory illnesses

RNA: Ribonucleic acid

NIRVs: Non-influenza respiratory viruses

PhD: Doctorate of philosophy

PCR: Polymerase chain reaction

PRISMA: Preferred reporting items for systematic reviews and meta-analyses

SARI: Severe acute respiratory illness

URIs: Upper respiratory illnesses

WASH: Water, sanitation and hygiene

WHO: World health organization

WRAIR: Walter Reed Army Institute of Research

ABSTRACT

Background: Acute respiratory tract infections (ARTIs) of viral origin lead to substantial morbidity and mortality. Human respiratory syncytial virus (HRSV), human parainfluenza virus(HPIV), and human Adenoviruses (HAdV) have been frequently identified in the ARTIs. These viruses have severely threatened young children, the elderly, and immunocompromised people, causing significant public health burdens and outbreaks. HRSV, HPIV, and HAdV triggered epidemics vary by geographical location, time, and virus type. The epidemiological evidence of HRSV, HPIV and HAdV are scarce in Kenya and the East Africa Community (EAC) region generally.

Objective: This retrospective investigation was conducted to define morbidity burden, estimate prevalence, and determine socio-demographic, clinical characteristics and climatic factors associated with HRSV, HPIV and HAdVs infections in Kenya. Besides, it assesses seasonality and described the spatiotemporal distribution of HRSV, HPIV and HAdVs.

Methods: A retrospective cross-sectional investigation was designed for the study period of 2007 – 2013. Secondary data of influenza-like illness (ILI) participants were gathered from the ILI surveillance system of Kenya. A convenience sampling strategy was done, ILI participants N= 17,261 from surveillance program of influenza and other respiratory viruses consisted this investigation target population. Prior, a systematic review and meta-analysis were carried out in EAC with a particular focus on Kenya for the period of 2007-2020 to pool the prevalence for HRSV, HPIV and HAdVs. To define morbidity burden, estimate prevalence, and assess seasonality, an exploratory analysis was performed based on the ILI dataset, followed by a descriptive analysis. Furthermore, a fitted logistic regression model was applied to determine significant factors associated with HRSV, HPIV, and HAdV infections. Kulldorff's spatial scan statistic and geographical information system (GIS) were used to describe HRSV, HPIV and HAdVs distribution patterns over time and space.

Results: For the systematic review, a total of 12 studies met the eligibility criteria among the studies documented from 2007 to 2020. The pooled prevalence was 13% HAdVs, 11% HRSV and 9% HPIV in the EAC partner states with available data.

In Kenya, the ILI surveillance program had eight surveillance sites from January 2007 to December 2013. The ILI morbidity burden for HRSV was 3.1%, HPIV 5.3%, and HAdV 3.3%. Infants (OR>1) were more likely to be infected with these viruses compared to other age groups. The participants' enrolled in the ILI surveillance system presented with several clinical signs. After adjusting for age, none of the clinical characteristics, except for fever and cough, were significantly associated with HRSV, HPIV, and HAdV infections. HRSV exhibited seasonality with high occurrence in January-March (Odds Ratio [OR] =2.73) and April-June (OR=3.01). Hot land surface temperature (≥40°C) was also associated with HRSV infections (OR=2.75), as was warmer air temperature (19-22.9°C) (OR=1.68) compared to cooler air temperature (<19°C). Moderate rainfall (150-200mm) areas had greater odds of HSRV infection (OR=1.32) than low rainfall (<150mm) areas. HRSV, HPIV, and HAdV cases were distributed in several counties and varied geographically. The HRSV cases were densely found in Western, and Coastal regions. Whereas, HPIV and HAdVs were identified in the coastal, central, and western regions.

Furthermore, the three respiratory viruses had local clusters with significant positive autocorrelation in the Western region of the country with ($P<0.05$). The primary purely spatial clusters of HRSV, HPIV and HAdV occurrence were found in the Western region. Besides, the space-time analysis indicated that HPIV primary cluster persisted in the Western region over the study period of 2007 to 2013. However, HAdV and HRSV primary clusters were observed in the Coastal region during 2008-09 and 2009-11 respectively. These results should be interpreted with caution because they were limited to the time of the study and could not be extrapolated to the actual population. Nevertheless, this investigation had the capability of including a large sample size, a lengthy study period, and a broad geographic region covering the entire country. The findings filled a substantial gap in the understanding of HRSV, HPIV, and HAdV epidemiology, providing resourceful information for intervention planning.

Conclusions and recommendations: Based on the systematic review of studies in EAC, the findings of this investigation indicated that human adenoviruses, human respiratory syncytial virus and human parainfluenza virus are prevalent in Kenya, Tanzania, and Uganda. These three respiratory viruses contribute substantially to ARTIs in the EAC partner states with available data, particularly among those with severe disease and those aged five and above.

However, ILI surveillance in Kenya for HRSV, HPIV, and HAdVs indicated that these three respiratory viruses contributed to ILI morbidity burden, and infants were significantly affected. HRSV had a clear seasonal pattern and was associated with climate parameters, contrary to HPIV and HAdVs in Kenya. Fever, cough and runny nose were at a high proportion among the ILI participants. Also, the findings of this investigation suggested that the hotspots (clusters) for RSV, HPIV, and HAdV occurred in the Western and Coastal regions of Kenya from 2007 to 2013. The Western region appeared more prone to the occurrence of the three respiratory viruses irrespective of the time.

Continued surveillance for HRSV, HPIV, and HAdVs is recommended to monitor changes in morbidity caused by these non-influenza respiratory viruses to the population in Kenya. Also, an event-based surveillance system should be established in the western and Coast regions to capture the occurrence of HRSV, HPIV, and HAdVs outbreaks. Furthermore, surveillance should include the population of all age categories with a particular focus on the elderly because there is a shortage of knowledge relating to this population.

CHAPTER I: INTRODUCTION

1.1. General background

Respiratory viruses are linked to a significant public health burden and the possibility of outbreaks or pandemics [1,2]. The world's largest pandemic of respiratory disease occurred in 1918-1920 when the influenza virus spread across the world and killed 50 million people [3]. Currently, the world is in the midst of a coronavirus disease of 2019 (COVID-19) pandemic caused by the Severe acute respiratory syndrome coronavirus 2 (SARS-COV-2), a respiratory virus that has infected 172.59 million people and killed 3.66 million people as of May 2021 [4]. Influenza and other respiratory viruses can be identified in 80%–95% cases of acute respiratory tract infections [5]. Human respiratory syncytial virus (HRSV), human parainfluenza (HPIV), and human adenoviruses (HAdV) are among the non-influenza respiratory viruses (NIRVs) that are known to contribute significantly to the burden of acute respiratory infections and cause sporadic outbreaks [6,7].

HRSV was first identified in a colony of coryza-afflicted chimps in 1956 [8]. Later it was isolated in infants with respiratory illness, and school-aged children who presented with the antibodies against HRSV [9,10]. HRSV has a linear single-strand RNA genome and is classified as a member of the *Mononegavirales* order, which includes the human parainfluenza virus [11]. HRSV belongs to the family of *Pneumoviridae* in the genus of *Orthopneumovirus.* The HRSV has enveloped RNA genome of ~15,000 nucleotides encodes 11 proteins [12]. These proteins include two major surface glycoproteins known as fusion (F) protein and glycoprotein (G) used for attachment. A variation in the glycoprotein (G) distinguishes two main classes of HRSV strains as strains A and B [13]. Other proteins include nonstructural, regulatory, ribonucleocapsid, and inner envelope matrix proteins [12]. The full genome nucleotide sequence analysis resulted in the identification of 11 RSV-A and 23 RSV-B genotypes [14]. During epidemic seasons, multiple genotypes have been observed co-circulating, suggesting that new genotypes can replace previously dominant strains.

HPIV was discovered in the 1950s and is divided into four types: 1, 2, 3, and 4 [15]. HPIV is also a member of the *Mononegavirales* order, which is part of the *Paramyxoviridae* family, which includes the *Respirovirus* and *Rubulavirus* genera [11]. HPIV is a negative-sense single-stranded RNA virus and causes respiratory diseases in humans and animals[16]. The four types HPIV-1 to HPIV-4 have six similar structural proteins encoded by the genome, except for the phosphoprotein which varies across the types[15]. HPIV-1 and HPIV-3 belong to the *Respirovirus* genus, whereas HPIV-2 and HPIV-4 are in the *Rubulavirus* genus. The genome length is ~ 15,000 nucleotides encoding six major structural proteins [17].

Besides HRSV and HPIV, the *Adenoviridea* family found in the order of *Rowavirales* is associated with respiratory illnesses [18]. HAdVs were isolated in 1953 and classified in the genus *Mastadenovirus* and constitute the seven known HAdV species or groups [19]. The species vary from HAdV-A to HAdV-G and cause a range of syndromes including hepatitis, myocarditis, pneumonia, gastroenteritis, and conjunctivitis [20–22]. Adenoviruses are non-enveloped double-stranded DNA viruses. DNA similarity between HAdV groups ranges from 48 % to 99 %, with less than 20% between HAdV subgroups [23]. The HAdVs genome is ~ 30- 40Kb and is surrounded by non-enveloped capsid [24].

In various parts of the world, the health burden of acute respiratory infections caused by HRSV, HPIV, and HAdV has been well reported [25–27]. These respiratory viruses have been reported in severe childhood pneumonia requiring hospitalization in Africa and Asia, whereas HRSV was the leading cause with 31.1% in all viral etiologies [7]. In general, the economic impact of viral respiratory tract infection that is not influenza-related is unknown. However, data suggests that the overall economic burden of non–influenza-related viral respiratory tract infections in the United States is in the range of $40 billion per year, with $17 billion in direct costs and $22.5 billion in indirect costs [28].

HRSV infections have been shown to have a long-term socioeconomic and health effect [29–31]. In 2015, the global prevalence of HRSV was 33.1 million in children under the age of five, with overall lower respiratory infection mortality ranging from 94 600 to 149 400 [26]. In 2016, HRSV was the second leading cause of lower respiratory infection mortality, with 76 612 (55 121–103

503) deaths worldwide, with 54 % of deaths occurring in children under the age of five [32]. HRSV infections cause 487, 247 outpatient visits, 17,799 hospitalizations, and 8,482 deaths per average season in adults and the elderly, according to a study from the United Kingdom [33]. In Australia, the economic burden of HRSV was estimated to be between $24 and $50 million of overall annual healthcare costs [34]. HRSV-triggered outbreaks have also been linked to serious disease consequences, such as patient hospitalization, intubation or artificial ventilation, admission to an intensive care unit, and death [35,36]. The outbreaks have been reported in all age groups for healthy individuals, and people with other health conditions [37,38].

While HRSV is a common cause of acute respiratory infections, HPIV and HAdV also cause societal and public health problems [39,40]. In different countries, there is increasing evidence for both HPIV and HAdV, indicating a substantial public health burden [41]. HPIV global burden estimates in children under the age of 5 years with acute lower respiratory tract infections (ALRTIs) were described in 2018. Thus, there were 29.5 million (21% cases of ALRTIs) HPIV cases in children below 5 years, 1.0 million (6–20%) hospitalizations, and 53,000 (7%) deaths due to HPIV [42] indicating that HPIV contributes substantially to the childhood respiratory disease burden. In Asian countries, where the prevalence ranges from 1% to 66%, HPIV-3 is the major dominant virus type [43]. Similar evidence was described in the adult population. HPIV prevalence ranged from 2.14% to 27% in a Brazilian study, with 74.23% prevalence in children under the age of one year [44]. Similar observations have been made in several studies carried out in various countries, in which HPIV 1-4 types were widely spread [45,46]. The cost associated with HPIV infections is less studied worldwide than RSV. In the United States, however, from 2004 to 2010 annual costs for HPIV-associated croup, bronchiolitis, and pneumonia hospitalizations of children under the age of five were estimated to be $43 million, $58 million, and $158 million, respectively [47]. Amongst HPIV types that have been identified during outbreaks, HPIV-3 is the most common cause of confirmed HPIV infection [48–52]. HPIV nosocomial infections are a serious concern to immunocompromised patients and may result in outbreaks.

HAdVs have sparked public health concerns about new and re-emerging strains that have the potential to cause large outbreaks and serious pneumonia in immunocompetent adults and children [53,54]. In the United States, some Asian countries, including China, and Europe, outbreaks of novel HAdV serotypes have been identified [53–60]. HAdV primarily causes outbreaks in areas with crowding, such as schools, military barracks, and home care environments, among other places [55,59,61]. Over the last ten years, a growing number of cases of community-acquired and serious pneumonia linked to HAdV have been reported in different countries [62–64].
However, the lack of the estimated global burden of HAdV-related respiratory diseases, as well as insufficient evidence from developing countries, leaves gaps in our understanding of the evolving environment.

1.2. Statement of the problem

HRSV, HPIV, and HAdV, all play a role in the development of upper and lower respiratory syndromes, including pneumonia, which is the leading cause of death in infants, the elderly and people with compromised immune systems [7,65]. Although influenza-like illness (ILI) and severe acute respiratory illness (SARI) surveillance systems can detect non-influenza respiratory viruses (NIRVs), these systems were created mainly to monitor influenza virus activity with NIRVs receiving less attention [66,67].

The WHO's Battle Against Respiratory Viruses Initiative (BraVe) has acknowledged the growing evidence for NIRVs' public health significance, emphasizing the need to use available surveillance systems to assess a wider range of respiratory viruses [1,40]. Viruses are found in a high percentage of acute respiratory tract infections (ARTIs) and cause a variety of upper and lower respiratory tract syndromes, such as acute otitis media, croup, pneumonia, bronchiolitis, and asthma [68–72], and although co-infection with both respiratory viruses and bacteria is known to occur, they are infrequently reported. While NIRVs' role in respiratory disease is recognized, the complexities and breadth of illnesses caused by these viruses are poorly understood [40], making it difficult to determine which viral agents are responsible for which syndromes, as well as assigning the cause of severe ARTIs due to mixed virus infection [73–75].

Although non-pharmaceutical interventions and some other medical efforts are effective in controlling all viruses, the identification of dominant viral pathogens is necessary to target vaccines and therapeutics to most effectively control outbreaks and protect public health at the population level.

ARTIs of viral origin has increased in prevalence since the establishment of acute respiratory infection (ARI) surveillance programs across Sub-Saharan Africa in 2006 [67]. These surveillance programs were developed in response to the 2005 International Health Regulations (IHR) for tracking emerging respiratory viruses, with a particular emphasis on pandemic influenza viruses[76]. The threats posed by NIRVs have been documented, as have the various factors that influence the health outcome[6,65,73]. Among non-influenza respiratory viruses associated with ARTIs, HRSV, HPIVs, HAdV are frequently identified [77–80]. NIRV pathogens are present in people of all ages across Sub-Saharan Africa, and the majority of them cause severe ALRTIs in children under the age of five [40,81–89].

The World Health Organization Regional Office for Africa (WHO-AFRO) released Country Profiles (https://www.who.int/data/gho) in 2012, which revealed that among the top three causes of death in the East African Community (EAC) were acute lower respiratory tract infections (ALRTIs). ALRTIs in EAC partner states were identified in Tanzania (8.7%), Kenya (12.3%), Uganda (12.3%), South Sudan (12%), Rwanda (10%), and Burundi (12.5%). Whereas influenza viruses are known to cause a substantial proportion of respiratory infections, it is not clear how much the contribution towards ALRTIs is due to NIRVs. States with influenza and other respiratory viruses' surveillance programs recognized by the WHO include Kenya, Rwanda, Tanzania, and Uganda in the EAC [89].

The East African region's population is nearly 177 million inhabitants [90]. The population is highly integrated with the regional free mobility of the people, culture exchange, tourism, a common regional market, and other social exchange activities. All these factors have been described elsewhere to increase the risk of infectious disease transmission and spread [91]. ARTIs are endemic in the EAC region, this has been recognized in various studies reporting etiologies in respiratory syndromes surveillance [92–95].

In Kenya, influenza and other respiratory viruses' surveillance program were introduced in 2006. The country had two complementary systems that were designed to carry surveillance at district hospital surveillance (Known as sub-county hospitals after Kenya government devolution in 2010) and provincial hospitals surveillance (now called county hospitals). The two systems gave a robust, geographical, and population representativeness to investigate respiratory viruses in Kenya [96,97]. Although both systems provided a strong surveillance system in Kenya, and extensively investigated influenza viruses, they did not report the epidemiological findings from non-influenza respiratory viruses, leaving gaps in the knowledge of these important pathogens in the country.

1.3. Significance of the study

It is evident that an unknown proportion of respiratory infections is caused by HRSV, HPIV and HAdV in EAC including Kenya [98–101]. Whereas Kenya had simultaneous surveillance systems for which HRSV, HPIV, and HAdV were identified frequently, none had reported the burden of those NIRVs, factors driving the infections, hotspots areas, or timing for the interventions. As a whole, the epidemiology of those respiratory viruses has been sparsely documented.

The objectives in this thesis were designed to make use of data generated by the programs for influenza and other respiratory virus surveillance in Kenya to address the above-indicated gaps. They also document the epidemiological evidence of ILIs caused by HRSVs, HPIVs, and HAdVs in Kenya. These objectives further add to the body of knowledge by providing synthesized evidence of the prevalence of infections caused by HRSVs, HPIVs, and HAdVs in the entire EAC. The investigations provide a thorough understanding of HRSVs, HPIVs, and HAdVs' epidemiology in the first seven years of ILI surveillance in Kenya. The epidemiologic evidence presented here will inform decisions making, designing interventions, and planning prevention or control measures.

CHAPITER II: LITERATURE REVIEW

2.1. Rationale

2.1.1. Epidemiology of human respiratory syncytial virus, human parainfluenza virus, and human adenoviruses

Respiratory viruses are common throughout the world, although their prevalence varies over time and across geographical regions. HRSV is one of the most common causes of acute respiratory infections (ARTIs) around the world, especially acute lower respiratory tract infections (ALRTs) in children under the age of five and the elderly over the age of 65. Around 45% of childhood HRSV ALRTs result in hospitalization and death in infants under the age of six months, while 1–10 % of HRSV ARTIs are identified in adults[26,102].

HRSV has a high prevalence worldwide, according to several reports, particularly among young children under the age of five. In a study conducted in Latin America in 2013, the prevalence of HRSV infections in infants aged 1-6 months was found to be 41.5% in ALRTIs [103]. HRSV was responsible for 18.7% of ARTIs in China in 2015 [104] and a similar prevalence of 18.7% was registered in Iran in 2013 [105]. According to a systematic review conducted by the Western Pacific Region (WPR), HRSV was present in 16.73 % of ARTI patients[106]. RSV infections were found to be prevalent in 24.4 % of countries in the Middle East and North Africa (MENA) region [107].

In 2018, 14.6% of people with ARTIs in Africa were infected with HRSV [108]. In Sub-Saharan Africa, an estimated 131 million cases of community-acquired pneumonia were reported, with viral pathogens being the leading cause [109]. HRSV types A and B have been known to circulate independently with a slight predominance of type A; however, there was no difference in clinical outcome between the two types [110,111]. HRSV is widespread in Kenya, and several studies have documented the prevalence of HRSV from ARTIs[112–116]. According to the literature, HRSV affects people of all ages, but it has the greatest impact on children under the age of five. Similarly, HPIV exhibits similar trends, albeit, with fewer studies documenting the burden of associated diseases, this was also seen with HAdV [117–119].

The disease burden figures for HPIV childhood infections in Asian countries vary from 1 to 66 % [120]. During the surveillance period of 2006 to 2010, 3.2 % of people with influenza-like illness in Latin American countries had HPIV infections [121]. Over a surveillance period of 2010-2014, an HPIV prevalence of 8.0 % was also reported in the population with influenza-like illness in the United States[122]. HPIV is also one of the known etiological agents of pneumonia in Africa [109]. In Kenya, people with acute respiratory tract infections (ARTIs) had a 9 % HPIV prevalence [123]. HPIV-1, HPIV-2, HPIV-3, and HPIV-4 all cause a variety of respiratory illnesses, but HPIV-3 is the most common, causing severe morbidity and mortality [15,124]. Although the burden of diseases associated with HPIV is not well defined, the virus has been characterized from the genomes obtained from around the globe [125].

Certain HAdV species contribute to the aetiology of respiratory illnesses in humans [126]. Among the most common species are species B (serotypes 3 and 7), C (serotypes 1, 2, and 5), and E (serotype 4) [127–129]. HAdV serotypes are found all over the world. There is evidence of serotypes coexisting and infecting people [130–134]. Several surveillance programs have documented HAdV prevalence in various regions, indicating their disease burden in public health. Worldwide, HAdV-3 is the most common, accounting for 15% to 87 % of all HAdV respiratory infections, whereas overall HAdVs were responsible for 3.8 % of asthma exacerbations and 2.1 % of an acute exacerbation of chronic obstructive pulmonary disease (AECOPD) prior to 2017 [135–137]. In China alone, HAdVs were 12.0% prevalent in hospitalized ARTIs children from the southern part of the country and 6.33 % prevalent in children with ARTIs from the northern (Lanzhou) part of the country [56,135,138]. Through the ILI surveillance network, HAdV species circulating in Central and Southern Latin America were identified, and species belonging to the C, B, and E species were identified [139]. In Peru, the two major surveillance systems, ILI and SARI, discovered a 6.2 % prevalence of HAdVs [140]. Similar species of HAdVs have been characterized in Egypt, with a predominant circulation of HAdV-C, which is consistent with global trends of HAdV respiratory infections [141]. The surveillance system identified that 17.5 % of ILI cases were infected with HAdVs in Gabon, 21.7 % in refugee camps in Kenya, 30.8 % in Senegal, and many other countries [83,142,143].

HRSV, HPIV, and HAdV transmission modes of contact, direct (self-inoculation), indirect (fomites), and droplets (aerosols) allow these viruses to spread efficiently among humans [144,145]. These respiratory viruses primarily replicate in the respiratory tract and are shed in respiratory secretions (144). HRSV transmission between humans is known to primarily occur via fomites and droplets, but recent studies claim that HRSV can be transmitted via aerosols (145–148). Furthermore, in pediatric studies, the virus was found to be capable of crossing the placenta from the infected mother's lungs to the fetus, predisposing the offspring to long-term sequelae [146,147]. There is less evidence on the transmission modes of HPIVs (types 1–4) in particular. Only direct contact, indirect (fomites), and droplet transmission are known HPIV transmission modes [148]. HPIVs are more easily recovered from non-absorptive surfaces than from absorptive surfaces [15,149]. HAdVs are primarily transmitted through person-to-person contact, fomites, and, on rare occasions, airborne aerosols [150]. Several studies have shown that removing HAdVs from aerosols, skin, fomites, and environmental surfaces is difficult [151,152]. HRSV, HPIV, and HAdV all have slightly different incubation periods, ranging from 4-5 days to 2-3 days to 5-6 days, respectively [153,154].

Certain factors Influence the occurrence and transmission of HRSV, HPIV, and HAdVs from person to person [144]. Host behaviours such as overcrowding, daycare attendance, birth during the seasonal peak of infection, poor parental education, and breastfeeding hygiene are among the common demographic factors reported in various studies [155]. Furthermore, weather and climate; humidity, temperature, precipitation, and airflow all have an impact on the transmission of human respiratory viruses [155–158]. Although several factors may influence transmissibility, rate, and severity, respiratory virus infections may be associated with a broader range of interconnected host determinants [155]. Host determinants, primarily age, gender, and health status, are known predictors of severe infections [158,159]. Prematurity [160], congenital heart disease (CHD), neuromuscular impairment, bronchopulmonary dysplasia (BPD), immunodeficiency, Down syndrome, and ageing all play a role in severe respiratory infections [161–165]. Socioeconomic factors also play an important role in the outcome of respiratory viral infections [166]. Multiple births, poor parental education, maternal smoking or indoor smoke pollution, crowded households, young siblings, malnutrition, atopy or asthma in the family, and living at high altitude all increase the risk of a severe outcome [81,165,167–169].

HRSV-caused acute respiratory infections are most commonly reported in infants and toddlers with ALRTIs [170,171]. The risk of hospitalization was found to be lower in healthy infants, but significantly higher in premature infants and babies with chronic lung disease or congenital heart disease [172]. In 2015, the global mortality rate from HRSV infections was 59600, ranging from 48000 to 74500 in children under the age of five, with infants under the age of six months accounting for 45 % of deaths [26]. HRSV has also been described in elderly people, with 14 000 in-hospital deaths worldwide from HRSV-ARI ranging from 5000 to 50000. There is, however, a scarcity of related epidemiological data from developing countries [173]. Adults with HRSV were found to have higher attack rates and died at a higher rate in immunocompromised people [174,175]. Several studies have shown HRSV infection episodes occur in healthy adults but there is an increased risk in the elderly [13]. HPIVs are important pathogens in adults as well, with upper respiratory tract infections being the most common [176,177].

Besides, HPIVs can cause infections of the lower respiratory tract, especially in children under the age of five and people with compromised immune systems (180,182–184). It should be noted that HPIV-3 is the most common serotype and causes more hospitalizations in children under the age of five than HPIV-2 or HPIV-1. HPIV-4 is less common. Similar to HRSV, the most severe respiratory illness caused by HPIV-1, 2, 3 occurs in infants during their first months of life [178]. HAdVs cause respiratory tract infections in children as well, with severe infections occurring in immunocompromised patients [82,179–182].

In residential facilities such as military camps, home care, and other collective areas, fatal outbreaks of pneumonia caused by HAdVs have been reported [183]. Furthermore, there is an increase in the number of HAdVs deaths among children and the elderly [58,59,184–186]. Exposure to tobacco smoke, pollutants, poor breastfeeding, malnourishment, low maternal education, socioeconomic status, and daycare attendance all increase the risk of severe infections [187–190].

2.1.2. Seasonality of human respiratory syncytial virus, human parainfluenza virus, and human adenoviruses

Seasonality of acute viral respiratory tract infections is critical for recognizing timing and preparing interventions for prevention (vaccination) and control (treatments) steps [191]. Most acute viral respiratory infections have distinct seasonal patterns in temperate climates, with peaks during the winter months[192–194]. However, this seasonality is less noticeable in the tropics, where meteorological parameters fluctuate much less than in temperate climates [195–198].

The seasonality of HRSV varies greatly across geographical regions, years, and climate [199]. HRSV epidemics are recorded in temperate regions during the cold winter months, while in tropical countries in Asia, Africa, and South America, the peak of epidemics is correlated primarily with rainy seasons [107,200–202]. Nonetheless, HRSV epidemics have been observed during the dry season in regions south of the equator [203–205]. HRSV seasonal trends are predictable in both the northern and southern hemispheres. HRSV activity is predictable in that it is mainly restricted to the winter and late autumn in temperate regions, with an epidemic duration of approximately 5 months [206,207].

The length of HRSV epidemics in tropical African countries, including Kenya, has been shown to be 5 months, which is comparable to the temperate climate [197]. In the cold season, studies have shown that inclement weather affects human behaviour by reducing outdoor activities and increasing indoor crowding [208,209]. Such behaviours increase HRSV exposure and transmission. Another theory is that low temperatures prolong HRSV stability in fomites during the winter [210,211]. In the tropics, climatic factors such as humidity and temperature play an important role in HRSV seasonality; higher levels of humidity and stable temperatures are indicated to support large aerosol droplets, allowing HRSV transmission all year round [212,213].

The seasonal peaks of the four HPIV types differ geographically and over time [214]. HPIV epidemics appear to last slightly longer (6 months) than RSV (5 months) and occur in both hemispheres in the spring or early summer months [197]. In a temperate climate, seasonal peaks differ between HPIV types [215–217].

HPIV-3 is reported in the annual clear epidemic peak of later summer, in contrast to HPIV-1 and HPIV-2, which have marked epidemic peaks in a biennial early winter in the northern and southern hemispheres of temperate climes [216].

In the United States, for example, HPIV-3 causes annual epidemics in the spring and summer, whereas HPIV-2 co-circulates with HPIV-1 during the fall seasons and causes regular outbreaks [218,219]. Because HPIV-4 is reported to have a low prevalence, the seasonality of HPIV-4 is not well defined in the literature. However, a recent study conducted in the United States found a significant link between HPIV-4 and increased severity of illness in hospitalized children, which occurred in the early fall and late summer [220]. A larger study conducted in Brazil described HPIVs in the tropics, primarily indicating that HPIV-1 circulates during the fall, HPIV-3 peaked in the spring, and cases of HPIV-2 appeared throughout the year with peaks in the fall and early spring [221,222].

The seasonality of HAdV differs from that of RSVs and HPIVs, which tend to occur during the winter in temperate climates. HAdV infections occur all year with no evident seasonality, but in temperate climates, where peaks can be observed in late winter, spring, or early summer [223]. HAdVs infections are also detected throughout the year in tropical climates, with peaks of varying amplitude and less defined seasonality [77]. The duration of HAdV epidemics vary according to the viral species or serotypes and spread quickly in crowded populations [59,224–228]. HAdV epidemics have been reported in military training facilities, hospitals, boarding schools, nurseries, long-term care facilities, psychiatric centers, job training centers, public swimming pools, and other areas with crowding [228–235].

2.1.3. Clinical manifestations of viral respiratory infections caused by human respiratory syncytial virus, human parainfluenza virus, and human adenoviruses

Infections caused by RSVs, HPIVs, and HAdvs are difficult to distinguish clinically, as are infections caused by other respiratory viruses. There are many similarities between the respiratory syndromes caused by these viruses, which range from mild upper respiratory tract infections to severe lower respiratory tract infections [236]. Clinical manifestations differ depending on age, health status, and whether the infection is primary or secondary.

Upper respiratory tract infections typically present with a variety of mild syndromes. Upper respiratory tract infection caused by RSV is self-limiting, with symptoms including rhinorrhea, cough, sneezing, nasal congestion, myalgia and in some cases fever [237]. HPIVs have similar symptomatology [13,238], though disseminated HPIV infections present as uncommon neurologic, renal, and rheumatologic diseases affecting other organ systems [239]. HAdVs can also cause a mild upper respiratory infection that is usually self-limiting. Depending on the HAdV serotype, symptoms may include cough, rhinorrhea, pharyngitis, fevers, and conjunctivitis [240,241]. Other symptoms of HAdV infections present differently depending on the organ systems that are affected [241].

The common cold is not distinguished from other syndromes of viral upper respiratory tract infection by symptoms such as nasal stuffiness, mucus discharge, sneezing, coughing, and sore throat. It might be caused by a wide range of viral pathogens which infect the host's respiratory tract [242]. Pharyngitis is distinguished by the presence of three symptoms: fever, sore throat, and pharyngeal inflammation. Viruses are the most common causes of pharyngitis, accounting for 25-45% of all cases, with HAdV being the most common [243]. Otitis media caused by any of these viruses is characterized by middle ear-space infections that affect people of all ages but are most common in children aged 6 to 24 months [244,245]. Because of the wide range of clinical manifestations of upper respiratory tract infections caused by these viruses, illnesses caused by these viruses are commonly referred to as influenza-like illness (ILI), which is a standardized case definition developed by WHO to characterize influenza and other respiratory viruses infections.

ILI is defined as an acute respiratory illness with a fever of 38 °C or greater and a cough that began within the previous 10 days [246]. Other intrinsic symptoms of ILI may include headache, malaise, nausea, body aches, and loss of appetite. These manifestations, however, differ in children, adults, and the elderly, depending on whether they are healthy or have comorbidity conditions [247].

The infection of the lower respiratory tract has distinct severe manifestations. Croup, also known as laryngotracheal-bronchopneumonitis, is an inflammation of the trachea, larynx, and bronchi that causes a barking cough and stridor. On days 3 or 4, it appears to be upper respiratory tract infections with a low-grade fever and dysphagia; however, severe symptoms may appear later if the infections persist for up to 7 days [248]. HPIVs are the most common cause of croup, accounting for 75% of respiratory infections with this symptom [249]. Nevertheless, other respiratory viruses, such as RSVs, HAdV, and influenza viruses, have also been linked to croup outbreaks [249–252].

Viral bronchiolitis is a type of respiratory syndrome that affects the lower respiratory tract. It refers to the obstruction of the lower respiratory tract caused by inflammation of the small airways (bronchioles) [253,254]. The infection is characterized by oedema, excessive mucus production, and epithelial cell necrosis [255]. Patients typically first present with ILI symptoms within a few days. With continued infection, fever, tachypnea, expiratory wheezing, retractions, and air trapping may develop [254]. The syndrome is most commonly reported in infants and then declines in school-aged children. Bronchiolitis symptoms in infants have been reported to last anywhere from 15 days to 3 weeks [13]. Although other viruses, such as HPIVs and HAdVs, can cause similar clinical features, HRSV is the most common virus responsible for bronchiolitis cases in children [256].

Pneumonia caused by viruses has been distinguished from other viral lower respiratory tract syndromes. In pneumonia cases, fever and rales are common, and pulmonary consolidation is common [257]. Infection of viral pathogens in the lung parenchyma causes abnormalities in gas exchange at the alveolar level and inflammation, resulting in viral pneumonia [258]. HRSV pneumonia affects people of all ages, but it is usually severe, with a high rate of occurrence in the elderly and immune-compromised people [237,259]. Although HRSV typically affects infants and

young children, bronchiolitis, rather than pneumonia, is the more common severe syndrome. Clinically, HRSV pneumonia is distinguished by wheezing, which is a characteristic of advanced viral infections [259,260]. However, there is no single clinical sign that can predict which viral pathogen is causing pneumonia [261]and only improved laboratory diagnostics can improve the identification of old and new viral pathogens [262]. HPIV pneumonia is characterized by typical symptoms such as cough, fever, and rales with pulmonary consolidation. All four HPIV serotypes have no distinguishing clinical features, though HPIV3 is most commonly associated with severe pneumonia [215,262]. Following upper respiratory tract infections, HAdV pneumonia is usually mild in immunocompetent individuals and symptoms can resolve in 2 weeks [257,259]. Severe adenoviral pneumonia, on the other hand, has been reported sporadically in immunocompetent people [263], and more frequently in immunocompromised patients [264,265].

The case definition of severe acute respiratory infection (SARI) was refined in 2011 [266], adopting the definition from the integrated management of childhood illness strategy to specify both pneumonia and severe pneumonia caused by influenza viruses, as well as related diseases such as asthma exacerbation and chronic obstructive pulmonary disease (COPD) [267,268]. WHO's standardized case definition of SARI for all age groups is: an acute respiratory illness with a history of fever or measured fever of 38 °C and cough, requiring hospitalization within the previous 10 days [266].

Both ILI and SARI case definitions have been expanded through WHO Battle Against Respiratory Viruses (BraVe) initiative in 2012 to include non-influenza respiratory virus infections, allowing HRSV, HPIV, and HAdVs infections and related diseases to be assessed[40,269,270]. Although incubation periods may be used to differentiate respiratory infections, this is difficult because of the similar incubation periods among the viruses, the variation among types or serotypes of the same virus, and the effects of host factors such as age and health status [153]. The incubation period for RSV ranges from 3 to 7 days, with a 5-day average [153,237]. The HPIV incubation period is shorter, ranging from 2 to 6 days with a mean of 4 days, whereas HAdV incubation lasts 4-8 days with a mean of 6 days [153].

2.1.4. Diagnosis of the respiratory syncytial virus, human parainfluenza virus, and human adenoviruses' infections

It is critical to correctly identify viruses responsible for respiratory tract infections in order to most effectively treat patients and control epidemics. In medical laboratories, traditional diagnostic tests for the rapid detection of viral antigens or antiviral antibodies are widely used [271]. Immunoassay and virus culture are two of the most commonly used traditional assays. The immunoassay methods include immunofluorescence assay or direct immunofluorescence assay (DFA), which detects viral antigens using a fluorescence-tagged primary or secondary antibody. It is simple to use, quick, and inexpensive, so it is commonly found in surveillance and clinical laboratories [272].

Furthermore, lateral flow immunoassay (LFIA) is a rapid detection method for respiratory viruses used at the point of care that is based on an immunochromatographic technology [273–275]. Other common immunoassay techniques include enzyme-linked immunosorbent assays (ELISAs) [251], the hemagglutination inhibition test, and the complement fixation test. Conventional virus culture/virus isolation [276], semiconductor quantum dots [277,278], and other related methods are examples of non-immunoassay methods. These latter techniques are used in biomedical and biological research.

With the development of molecular diagnostics for viral respiratory pathogens, new technologies for diagnosing respiratory viruses have advanced [279]. Several nucleic acid amplification tests (NAATs) based on viral amplification approaches have been developed, with the most well-known technique being the polymerase chain reaction (PCR), which can detect an individual or multiple respiratory viruses [280]. PCR allows for the rapid, accurate, and sensitive detection of respiratory viruses. This method has been modified to provide real-time results from single or multiplex PCR for RSV, HPIVs 1-4, and HAdVs [281]. Multiplex PCR is less expensive and easier to use than several uniplex PCR tests.

Currently, NAATs, as opposed to conventional virus culture, are the gold standard diagnostic techniques for respiratory viruses in clinical settings [282]. Loop-mediated isothermal amplification (LAMP), transcription-mediated amplification (TMA), nucleic acid sequence-based amplification (NASBA), multiplex ligation-dependent probe amplification (MLPA), strand displacement amplification (SDA), rolling circle amplification (RCA), and helicase dependent amplification (HDA) are some other molecular assay techniques that are amenable to respiratory virus detection [279–281].

Furthermore, next-generation genome sequencing technologies are robust high-throughput tools for the rapid characterization and typing of respiratory viruses. The Sanger technique, which was developed around 30 years ago, has resulted in the development of numerous sequencing principles [283]. The Sanger sequencing technique has recently been replaced by the advancement of whole-genome sequencing (WGS) using next-generation sequencing (NGS) technologies. These nucleotide sequencing technologies have resulted in the discovery of new pathogens, the identification of viral mutations, molecular surveillance, drug resistance, host immune response, and other related applications [284]. Although these tools have not yet been scaled for routine clinical diagnosis, devices to perform these techniques are expected to become more widely available for biomedical research and routine diagnosis in the near future [280].

2.1.5. Prevention, control and management measures for respiratory syncytial virus, human parainfluenza virus, and human adenoviruses' infections

With specific challenges, some general control and preventive measures for acute viral respiratory infections have been documented [285]. There is evidence that single interventions, such as vaccination or antiviral therapy, are insufficient to halt the spread of respiratory viruses [286]. A combination of several interventions, on the other hand, can be extremely effective in community and health care wards. As a critical public health measure, physical interventions such as hygienic measures (hand-washing) reduce the transmission of respiratory viruses [287]. Control measures such as aerosols and droplets precaution (wearing masks, gloves, and gowns), contact precaution (keeping a distance of one meter), and airborne precaution (air filtration) are critical interventions in health care settings or during epidemics to control the spread of respiratory viruses [286].

Immunization is effective in lowering respiratory virus infections, particularly in vulnerable populations [288]. RSV vaccines have been in development for over a half-century, but several issues have stymied the development of safe and effective vaccines [289]. The most serious issue reported for vaccines entering pediatric trials has been induced RSV-associated diseases, which raises ethical concerns [290,291]. With the advent of new technologies, there are approximately 60 candidate RSV vaccines targeting pediatric, maternal, and elderly populations [292], the majority of which are in the preclinical stage and only 16 of which have entered clinical trials [293]. Several approaches have been proposed for the development of RSV vaccines, some of which have been unsuccessful. Formalin-inactivated (FI)-RSV vaccine, live-attenuated RSV, subunit RSV, nucleic acid, and vector-based approach vaccines are among them [289,293].

Palivizumab was approved in 1998 for the prevention of severe RSV infections in high-risk groups such as premature infants, children with congenital heart diseases and children with other significant medical conditions [294]. Due to the lack of a licensed RSV vaccine, it is the only humanized antibody approved for RSV prevention. None of the HPIV vaccines being developed in collaboration with RSV as polyvalent or bivalent vaccines, as well as HPIV monovalent designs, have been licensed or approved for use in immunization [295–297].

The HAdVs vaccine was developed in 1971 for US military programs and was routinely used for AdV-4 and -7 immunization in the military until supplies ran out [298,299]. The US Food and Drug Administration licensed and reintroduced live unattenuated vaccines for AdV-4 and -7 in 2011, but there has been no approval for use in other populations, including children [300,301]. China, on the other hand, has been investigating the possibility of developing AdV-3, 7, 14, and 55 multivalent vaccines for both civilian and military populations [302,303].

According to current evidence, there is no cure for infections caused by HRSVs, HPIVs, or HAdVs [304]. Only palliative treatments, such as supplemental oxygen, corticosteroids, inhaled ribavirin, nebulized hypertonic saline, epinephrine, and other supportive care, are available [294,305–307]. The FDA has approved aerosolized ribavirin as an HRSV treatment for severe HRSV respiratory tract infections [308–310]. HN inhibitors or anti-hPIV agents have advanced in phase II clinical trials and have been developed and tested for host-directed therapy [311]. Immunotherapy for adenoviral infections with several small molecule drugs has reached clinical trials, and some are in the preclinical phase, making promising progress for adenovirus treatment [312,313]. For example, brincidofovir (BCV), a lipid conjugate of cidofovir, was used to treat adenoviruses in pediatric patients undergoing hematopoietic stem cell transplantation and was found to be less toxic [314].

2.2. Hypothesis

The primary hypothesis was that HRSVs, HPIVs, and HAdVs caused a substantial morbidity burden in ILI outpatients at the sentinel surveillance sites. The proportion of HRSVs, HPIVs, and HAdVs-caused ILIs varied across geographic regions and seasons in Kenya. The HRSVs, HPIVs, and HAdVs-caused ILIs were significantly associated with demographic determinants, seasons, and climatic factors. Alternatively, to the null hypothesis was that the morbidity burden among ILI patients in Kenya was not triggered by either HRSVs, HPIVs, or HAdVs, there was no geographical or seasonal variation, and had no associated factor.

2.3. Objectives

The broad objective of this project was to carry out a retrospective investigation of the epidemiology, clinical characteristics, and risk factors associated with ILIs morbidity caused by RSVs, HPIVs, and HAdVs in Kenya from 2007 to 2013.

The specific objectives were to;

a. Determine the prevalence of RSV, HPIV, and HAdV infections among ARTI patients in East African Community partner states with particular focus on Kenya from 2007 to 2020.
b. Describe the morbidity burden of RSV, HPIV, and HAdV-caused ILIs in Kenya from 2007 to 2013.
c. Assess the seasonality of respiratory infections caused by HRSVs, HPIVs, and HAdvs in Kenya from 2007 to 2013.
d. Determine demographic determinants, clinical characteristics, and climate factors associated with infections caused by HRSVs, HPIVs, and HAdVs in Kenya from 2007 to 2013.
e. Describe the spatiotemporal distribution of HRSV, HPIV, and HAdV infections in different geographic regions of Kenya over the same period.

2.4. Thesis structure

The first chapter (Chapter 1) of this thesis provides background information on human respiratory syncytial virus, human parainfluenza, and human adenoviruses-related respiratory diseases on a global, regional, and national scale, with an emphasis on Kenya. The second chapter is a review of the literature on HRSV, HPIV, and HAdV infections. Chapter 3 defines and delivers the materials and methods used in this project. This project's findings are presented in Chapter 4. Chapter 5 discusses the project's findings, available literature, conclusions, and recommendations. All of the references cited in this thesis are included in Chapter 6.

2.5 Study approvals

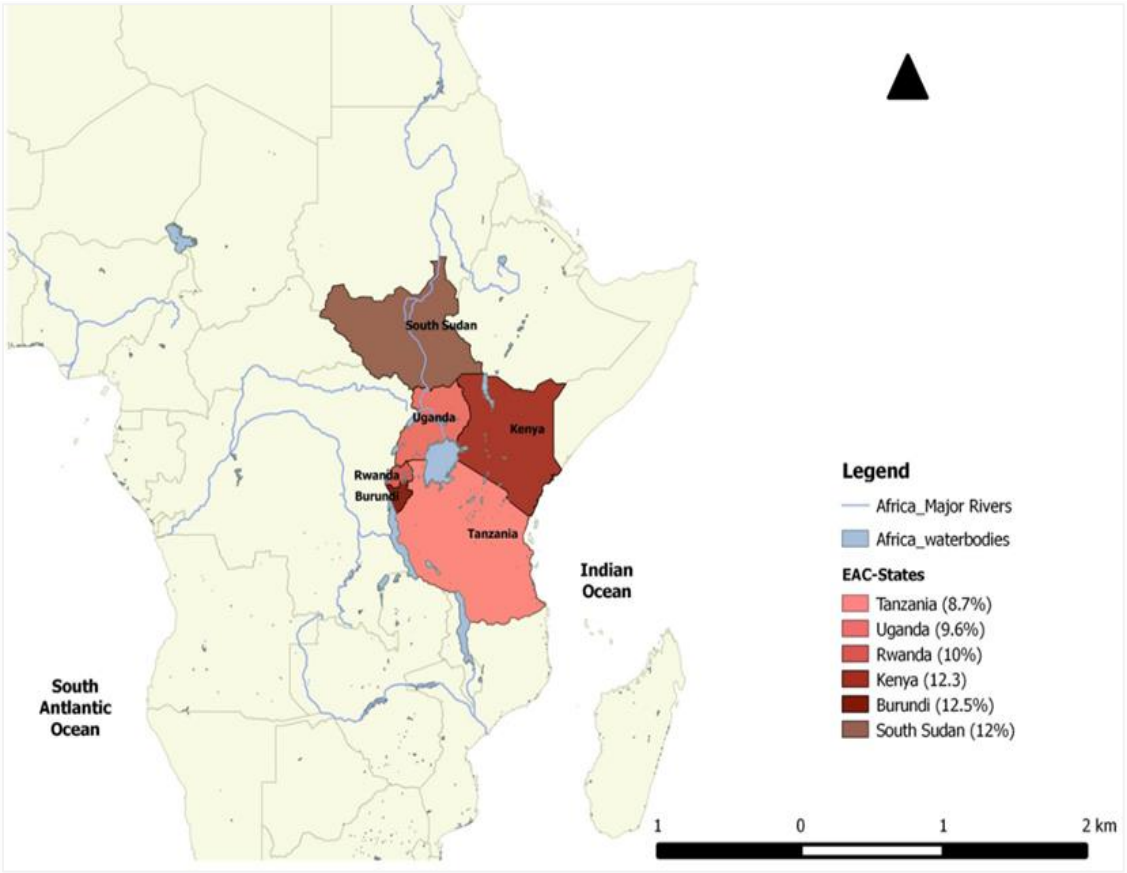
Ethical approvals for this project were obtained from Kenya Medical Research Institute (KEMRI) Scientific and Ethics Review Unit (SERU) with reference number KEMRI/SERU/CVR/003/3802 and the Walter Reed Army Institute of Research (WRAIR) with reference number WRAIR# 1267G.

CHAPTER III: MATERIALS AND METHODS

3.1. Study regions

The East African Community (EAC) is a regional integration comprising six partner states: Kenya, Tanzania, Uganda, South Sudan, Rwanda, and Burundi. According to the 2019 EAC statistics [90], it is home to approximately 177 million people. The EAC's population has become more integrated regionally as a result of migration, trade, social and cultural exchange, and other activities. Unfortunately, such activities have been shown to increase the risk of infectious disease spread [315]. Several studies have shown that different etiologies cause respiratory infections in the EAC region. Furthermore, acute lower respiratory infections (ALRTIs) are one of the top five causes of death (Fig 1) in East African Community member states [316–321].

Figure 1. The proportions of ALRTIs in East Africa Community partner states by WHO, 2012

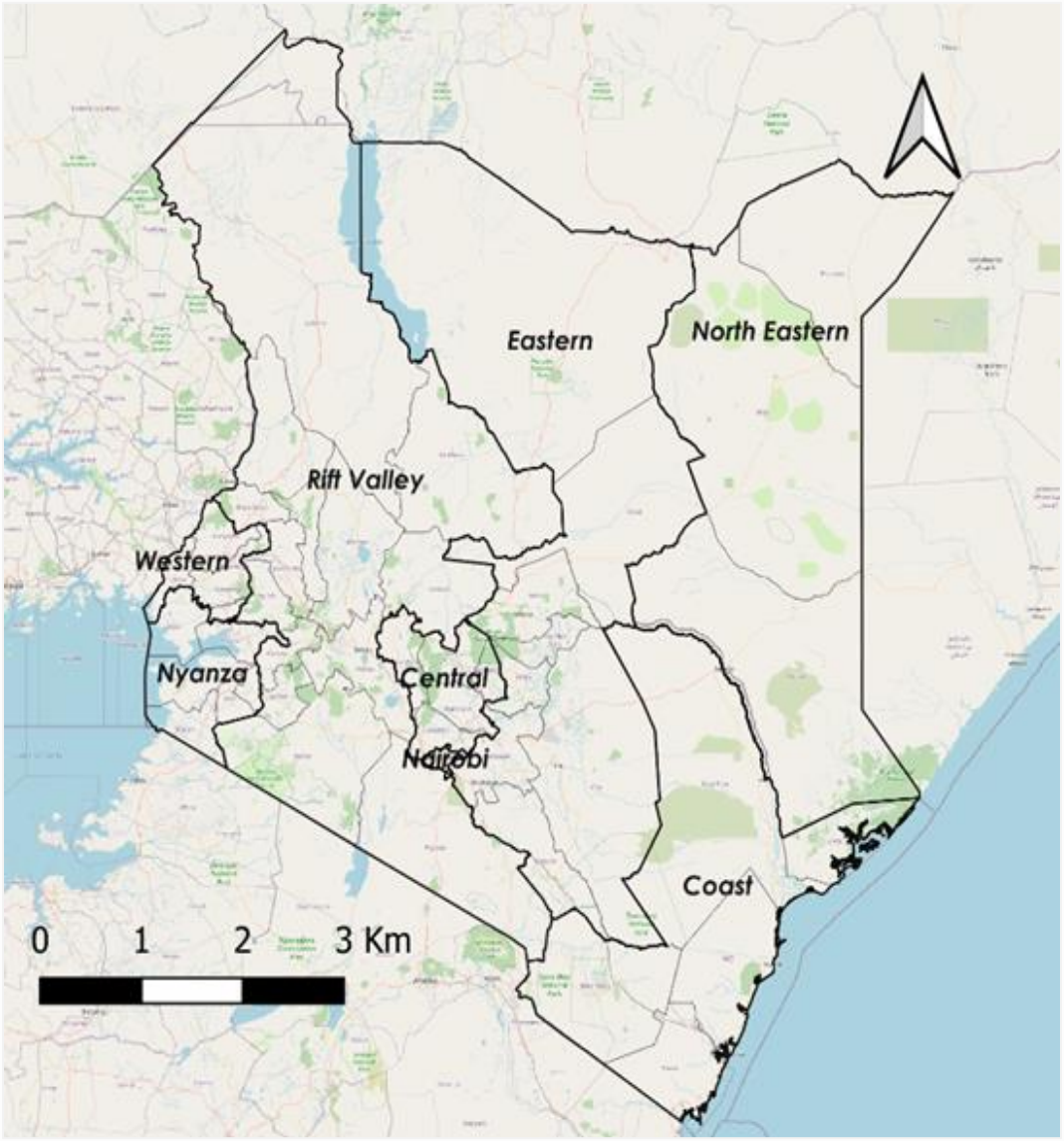


Kenya is located in Eastern Africa at a degree decimals -0.0236° S latitude, and 37.9062° E longitude with an area of 580,367 km²[322]. The country borders five countries including Uganda, Tanzania, South Sudan, Ethiopia and Somalia with the coastline of the Indian Ocean [322]. Kenya is bisected by the equator with one half of the country located in the northern hemisphere and another one in the southern hemisphere. Kenya had eight provinces subdivided into 158 districts [323] prior to the declaration of the new constitution in 2010. Later, the country was divided into 47 counties, comprising 290 sub-counties. The new geographical boundaries were incorporated into national administration in 2013. These regions were made up of counties that were previously constituting provinces (Fig 2), with their areas and populations based on the 2009 census [324].

Kenya's coastal region is made up of six counties covering an area of 79,686.1 km^2. The rift valley is Kenya's largest region, with fourteen counties covering an area of 182,505.1 Km^2. The Eastern region has the second largest surface area, with 140,698.6 Km^2 spread across eight counties. The North-Eastern region consists of three counties covering a total area of 127,358.5 Km^2. Furthermore, the central region of Kenya is made up of five counties covering an area of 11,449.1 km^2. The former Nairobi province is now Nairobi County, which houses Nairobi, Kenya's capital city, and has a small surface area of 694.9 km^2. Only four counties are represented in the Western-Nyanza region's surface area of 7,400.4 km^2 [324].

Kenya's population has grown at a rate of 2.2 over ten years, rising from around 38 million in 2009 to 47.8 million in 2019 [325]. HIV/AIDS and lower respiratory tract infections are major health threats to the population, causing high mortality and disability [316,326]. Lower respiratory infections rose from the third-leading cause of death in 2009 to the second-leading cause of death in the Kenyan population in 2019. However, HIV/AIDS remains the country's leading cause of death. Furthermore, the driving factors of major causes of death included malnutrition, unsafe sex, air pollution, and water, sanitation and hygiene (WASH) among others.

Figure 2. Geographical boundaries of Kenya regions



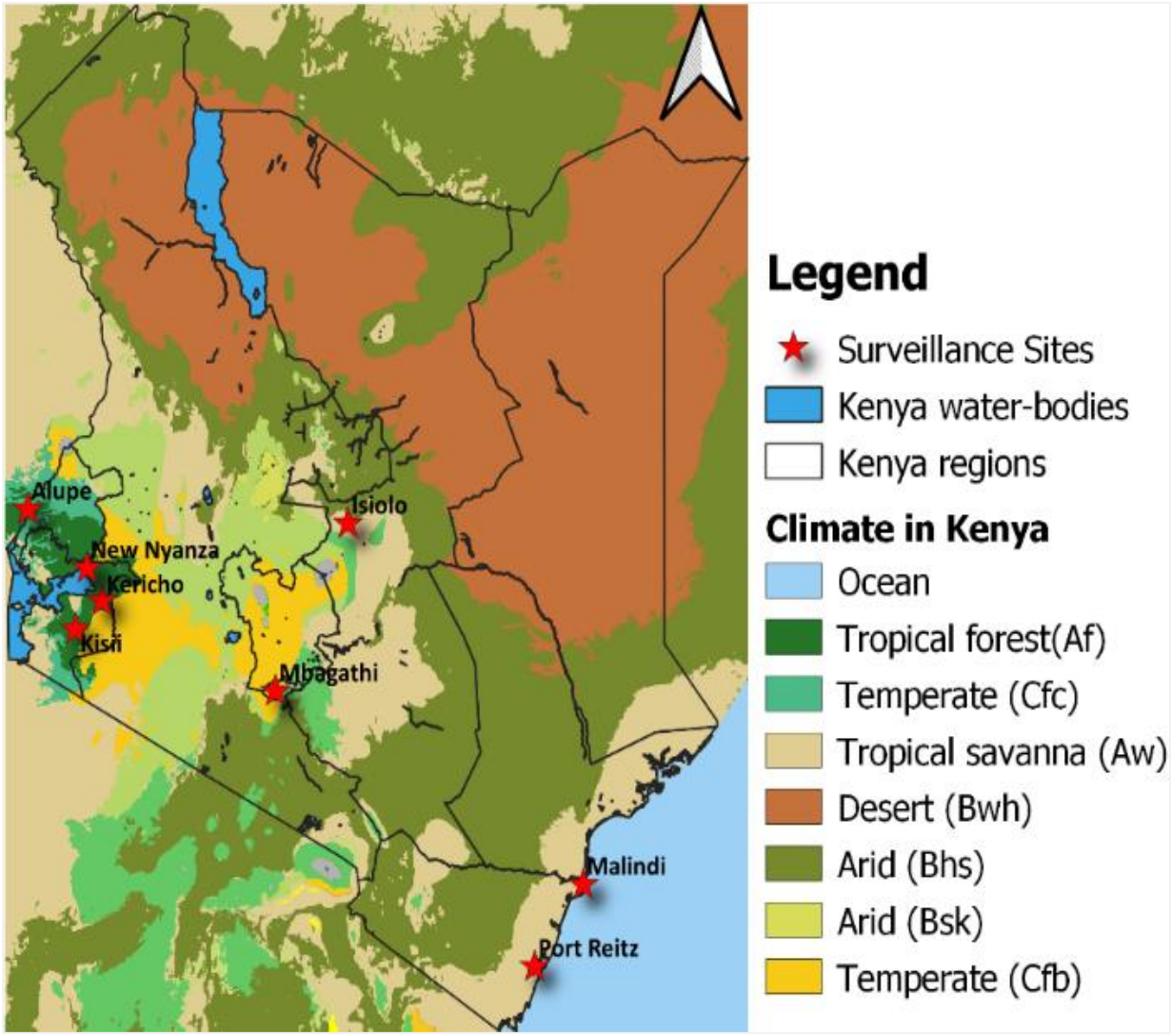
Kenya has a wide range of geographical features and climates. The country's physical characteristics are mostly equatorial, with environments ranging from arid to semi-arid. Furthermore, the country's topographical description shows distinct lowlands and uplands reliefs with varying landforms such as savannah, equatorial, glacial, aeolian, volcanic, and tectonic [327]. This topography has an impact on the climate, which ranges from extremely hot areas to cooler regions of the country. The climate in the northeast of Kenya is a hot desert, which converts to arid regions and becomes cooler toward tropical savanna climes in the coastal region.

The rift valley region has a distinct climate, ranging from the hot desert of the arid region in the north to the cooler tropical savanna of the central and southern rift valley regions. The climate of the country's western region ranges from tropical forest climate to temperate savanna climate. The current Köppen-Geiger climate classification system at a 1-km resolution [328] displays the different climatic locations of study regions created in qGIS 3.8.1-Zanzibar on a map of Kenya regional boundaries and ILI surveillance sites (Fig 3).

The average temperature in Kenya's coastline region is 22-30°C, with annual rainfall ranging from 20mm to 300mm [329]. According to climate records, the average temperature in the northern parts of the rift valley region ranges from 10°C to 28°C, with temperatures reaching 40°C and higher in the deep arid areas. Annual rainfall in the region ranges from 500mm to 3000mm, with a significant increase in the central region [330]. The climates of the Eastern and North-Eastern regions of Kenya are more similar. In the north, both regions receive little rain, with annual totals ranging between 250mm and 500mm. Aside from the hot temperatures ranging from 20°C to 40°C. The annual precipitation in the southeastern zone, on the other hand, is approximately 3673 mm [329,331,332].

The central region is cooler, with temperatures ranging from 14°C to 28°C and annual moderate rainfall ranging from 1016 mm to 2540 mm [333]. Nairobi has nearly identical climate characteristics, with a mean temperature of 19°C and an average annual rainfall of 958 mm [334]. The Western region receives rainfall all year, with a maximum annual rainfall of 2087 mm, and temperatures ranging from 14°C to 36°C [328]. The Nyanza region, which borders the Western area, has a similar climate [329]. Surveillance sites for ILI are geographically distributed across these regional climates. Only the hot desert, which had a low population density and was less accessible, lacked an ILI surveillance site. Eight surveillance sites represented the target population in the regions previously reported with respiratory infections.

Figure 3. The present Köppen-Geiger climate classification of Kenya.



3.2. Study population

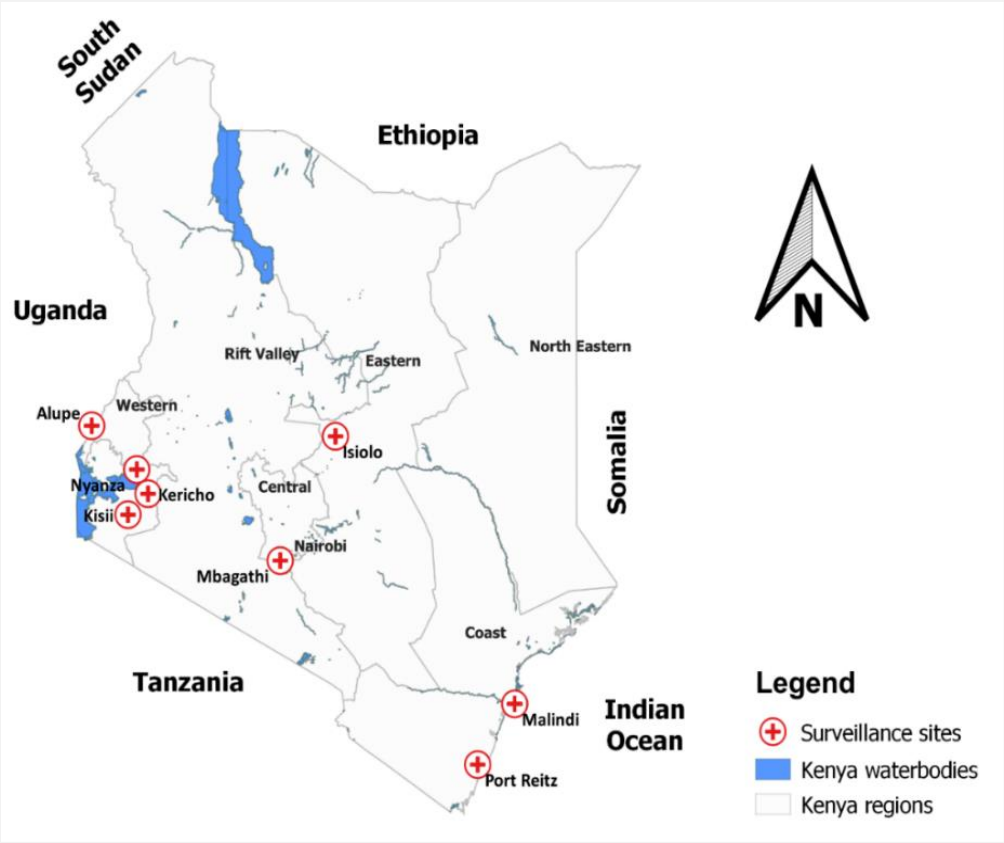
The ILI participants' origin. The study population consisted of ILI participants recruited under the ILI surveillance system in Kenya. The ILI participants were the outpatients who presented symptoms that met the case definition and were reported at the surveillance sites [267]. The sites for ILI surveillance were chosen based on regional population variation, disease incidence reporting, the frequency of international movement through the site, and the region's security situation. Kisumu (New Nyanza referral hospital-level 5), Nairobi (Mbagathi sub-county hospital-level 4), Kilifi (Malindi sub-county hospital-level 4), Mombasa (Port Reitz sub-county hospital-level 4), Isiolo (Isiolo sub-county hospital-level 4), Kisii (Kisii county hospital-level 6), Kericho (Kericho sub-county hospital-level 4), and Busia (Alupe sub-county hospital-level 4) were among the counties where the surveillance system was implemented.

The ILI surveillance system. This retrospective investigation used secondary data of ILI participants. The ILI participants secondary data constituted the ILI surveillance database and included demographic, clinical and laboratory records. The ILI database was hosted under the protocol of influenza and other respiratory viruses' surveillance program. The ILI surveillance system was implemented at eight surveillance sites of influenza and other respiratory viruses' surveillance program network (Fig 4). This retrospective investigation was nested under the surveillance program. Before the implementation of the ILI surveillance system, clinical officers were hired and trained to conduct ILI surveillance following the KEMRI Scientific and Ethics Review Unit (SERU), and the WRAIR Institutional Review Board (IRB) approved ethical principles. A clinical officer was assigned to each surveillance site to enrol study participants and collect data as well as specimens. From 2007 to 2013, participants in outpatient settings were enrolled if they met the ILI case definition and consented to be enrolled. Before sampling, informed consent was obtained from all participants in either English, Kiswahili, or a language understood by the participants. Participants under the age of 18 were consented to by their parents or guardians. Enrollment took place during working hours on Mondays, Wednesdays, and Fridays. Every day, a maximum of five participants were eligible for recruitment at each surveillance site.

The ILI participants' records. A questionnaire was designed and given to each participant. Each participant had a record of demographic information including age, gender, residence (city or village, district, province, estate or neighbourhood), occupation, workplace, and travel history. Clinical information was also recorded including cough, fever, sore throat, difficulty of breathing, chills, muscle aches, retro-orbital pain, malaise, vomiting, neurological, abdominal pain, nasal stuffiness, runny nose, sputum production, joint pain, fatigue, diarrhoea and bleeding. The laboratory result records were combined with demographic and clinical data to form secondary data for all ILI participants enrolled in the surveillance system.

The ILI laboratory methods for HRSV, HPIV, and HAdV diagnosis. The nasopharyngeal specimens collected from each participant were tested for respiratory viruses including HRSV, HPIV, and HAdV. A series of assays were used to perform laboratory diagnoses of these respiratory viruses. Initially, respiratory viruses were isolated using a viral culture (VC) technique. The samples were inoculated into cell lines to detect the presence of viral antigens. A confirmatory laboratory test was performed using polymerase chain reaction (PCR), which allowed for the detection of viral antigen nucleic acid in ILI samples. The ILI surveillance system tested a total of 17,621 samples. Each participant's laboratory results were recorded in an ILI-specific Microsoft Access database.

Figure 4. Influenza and other respiratory viruses program surveillance sites



3.3. Study period

While the World Health Organization Global Influenza Surveillance and Response System (WHO-GISRS) was established in 1952 [335,336], it did not include the majority of the world's countries for a long time. The WHO-GISRS monitors the activities of influenza viruses in order to make recommendations on laboratory diagnostics, vaccine formulations, antiviral susceptibility, and risk assessment. Furthermore, it acts as a global warning system for the emergence of influenza viruses with pandemic potential [335].

In response to the 2005 international health regulations (IHR), the WHO-GISRS network grew gradually, with several nations and partners establishing national influenza surveillance programs across Africa. Since 2006, national surveillance programs for Influenza-like Illness [ILIs] and Severe Acute Respiratory Illness [SARI] have increased from 21 to 127 and 2 to 98, respectively [337].

Prior to 2006, Kenya had no comprehensive surveillance of viral respiratory illnesses, including influenza viruses. The emergence of a pandemic threat in 2003 due to the highly pathogenic influenza A (H5N1) virus caused widespread concern [338]. As a result of this concern, Kenya established a surveillance program for influenza and other respiratory viruses. Several partners, including the Kenyan Ministry of Health (MoH), Kenya Defense Forces (KDF), Kenya Medical Research Institute (KEMRI), the Global Emerging Infections Surveillance (GEIS) program and WHO, partnered to establish a network of influenza and other respiratory virus surveillance programs in Kenya.

Specifically, influenza and other respiratory virus surveillance program in Kenya tracked emerging respiratory pathogens, with a focus on influenza viruses. Furthermore, the program identified important clinical characteristics of respiratory viruses in the general population. The program specifically identified changes in influenza virus subtypes and genotypes. To ascertain the effect of influenza virus strains on disease transmissibility, severity, and the efficacy of interventions such as treatments and vaccines. Other respiratory viruses, such as HRSV, HPIV, and HAdV, were also monitored as part of the same surveillance program.

The data generated by the surveillance program aided local and regional decision-making in prioritizing and implementing interventions on time. Furthermore, the surveillance activities expanded the KEMRI Influenza laboratory partnerships, and in 2009, the KEMRI Influenza laboratory became a national and regional WHO reference laboratory. This influenza and other respiratory virus surveillance system benefit the entire world by providing early warning of the spread of influenza and other respiratory viruses.

Since its inception in 2006, influenza and other respiratory virus surveillance program have been running for almost 15 years. Only from 2007 to 2020 did the program run two syndromic surveillance systems on a year-round basis. From 2007 to 2013, an influenza-like illness (ILI) surveillance system was in place, with a full-year calendar for every 12 months (January-December). In 2010, the program launched a parallel severe acute respiratory illness (SARI) system. However, the surveillance program for influenza and other respiratory viruses was hampered by a reduction in surveillance sites, funding, and the implementation of simultaneous

surveillance systems, resulting in inconsistency in the program. As a result, this retrospective investigation, which was nested within the surveillance program for influenza and other respiratory viruses, focused on the ILI surveillance system. From 2007 to 2013, ILI surveillance provided epidemiological evidence for HRSV, HPIV, and HAdVs which was reported through this investigation. This data improves pandemic preparedness and reporting capabilities, as mandated by the WHO 2005 IHR.

3.4. Sampling strategies

To obtain a sample size for this retrospective investigation, a convenience sampling strategy was used. This strategy allowed to access a larger sample size from the database of ILI surveillance system. The samples of ILI participants represented the ILI surveillance sites geographical location which was important for epidemiological evidence for HRSV, HPIV and HAdV infections in Kenya. The samples also represented the ILI surveillance timeline that led to the epidemiological trend of HRSV, HPIV and HAdV infections in Kenya.
As described by Ian Dahoo et al 2003, such non-probabilistic sampling strategies can be adapted to the type of analysis carried in this retrospective investigation. However, the limitations of the samples were discussed to provide clarity for better interpretation of the results.

3.5. Sample size determination

To study influenza and other respiratory viruses such as HRSV, HPIV, and HAdV, the WHO case definition for influenza-like illness (ILI) was adopted [267]. The ILI surveillance system enrolled 17,261 people from eight hospitals in Kenya's various regions. From January 2007 to December 2013, the hospitals served as ILI surveillance sites where study participants were recruited and registered. The ILI surveillance sample size was determined based on the laboratory's specimen processing capacity and funding availability.

All ILI participants recruited through influenza and other respiratory virus surveillance program were included in the target population of this investigation. Access to subjects from Northern areas was limited due to security concerns and low population density, but otherwise, the study population was a good representation of Kenya's diverse demographics and geographical regions.

Although, there are the basic concept of statistics which entails a representative sample size to estimate proportions. Based on the following formula; $N=Z^2PQ/d^2$ whereas, it is assumed that 50% is the expected prevalence, the desired sample size (N), the expected prevalence in the target population (P), the proportion of unknown respiratory viruses (Q=1-P), standard error (Z=1.96), and the level of statistical significance (d=0.05). Furthermore, the comparison of two proportions calculation applies with the formula; $N = \frac{[Z\alpha\sqrt{2pq} - Z\beta\sqrt{P1q1 + P2q2}]^2}{(P1-P2)^2}$ Where, Zα (the value required for 95% confidence is Z0.05= 1.96), Zβ (the value required for 80% power is Z0.80=-0.84), p (a priori estimate of the proportion), and p1, p2 (the estimate of proportion in the two groups) in an analytic study.

However, the surveillance program for influenza and other respiratory viruses had a larger sample size (N= 17,261 participants), which was efficient to estimate the proportion, define trends and perform a measure of associations. As a result, this investigation considered using the entire sample size drawn from the surveillance program for influenza and other respiratory viruses as a study population [339,340].

3.6. Source of data, and data management

The review dataset for the East Africa Community (EAC) was compiled from studies gathered through a systematic review and meta-analysis. The dataset included published studies and unpublished reports gathered between 2007 and 2020. The EAC partner states searched were Kenya, Tanzania, Uganda, Rwanda, Burundi, and South Sudan. Only, Kenya Tanzania and Uganda had available published and unpublished studies recorded in the dataset. To locate published studies in Medline and Global Index Medicus database, search engines such as PubMed, Google Scholar, and ScienceDirect were used. In addition, the EAC region's electronic databases for health and research institutions were searched (Annex 1). Furthermore, where necessary, the authors' correspondence was completed in order to verify and validate the data.

The author sourced unpublished data from these institutions in the EAC: Kenya Medical Research Institute (KEMRI-Kenya), Kenyatta National Hospital (KNH-Kenya), National Institute for Medical Research (NIMR1-Tanzania), Uganda Virus Research Institute (UVRI-Uganda), Makerere University (MAK-Uganda), Mulago Hospital (MUH-Uganda), Rwanda Biomedical

Center (RBC-Rwanda), and Institut National de Sante Public (INSP-Burundi). Other non-governmental public health research programs in the East African Community were also consulted for reports including those in South Sudan.

ILI dataset was extracted from KEMRI's influenza and other respiratory virus surveillance program's Microsoft Access database. The dataset contained data records for ILI participants from 2007 to 2013. All ILI participants' identification numbers, diagnostic results for HRSV, HPIV, and HAdVs (positive and negative), surveillance site location, time of illness onset, spatial information (residence, village, or estate), demographics (age, gender, occupation), specimen type (nasopharyngeal or oropharyngeal), date of specimen collection, and clinical characteristics were all included in the records (Annex 2). Furthermore, the dataset of laboratory-confirmed positive cases for HRSV, HPIV, and HAdVs were separately aggregated per time-series, surveillance sites, and counties. All these aggregates data were obtained by sourcing only positive cases from the ILI surveillance system access database. These aggregated data were compiled to perform trend analysis, distribution and clusters' analysis.

The additional datasets were obtained from a variety of sources. These datasets included Kenya population data per county, spatial coordinates, and climate data. The population per county dataset (Annex 3) included annual population counts data for each county that had at least one case of HRSV, HPIV, or HAdV during the surveillance period (2007-2013). The Kenya National Bureau of Statistics (KNBS) provided data on population per county based on national population censuses conducted in 1999 and 2009 [341]. Furthermore, county populations for 2007 and 2008 were derived from inter-census annual population projection data (1999-2009). Only the 2009 population census counts for that year were recorded from KNBS. However, the population data for the years 2010, 2011, 2012, and 2013 were derived from the inter-census (2009-2019) annual population projection [342].

The spatial coordinate dataset included each surveillance site's latitude and longitude (Annex 4), the location of the case's origin (estate or neighbourhood), and county centroids for case origin (Annex 5). These data were gathered from geocoded areas in Kenya using the Google Earth Pro tool [343]. The climate dataset included monthly mean land temperature data derived from Earth Observing System Moderate Resolution Imaging Spectro-radiometer (MODIS) measurements

aboard the Terra (EOS AM-1) spacecraft [344]. Furthermore, the rainfall data was obtained from the African Rainfall Climatology (ARC) and transmitted via satellite cold cloud [345]. The duration and daily rain gauge measurements were combined to produce a daily total rainfall product. The Global Historical Climatology Network provided monthly air temperature data compiled from various sources [346].

The time-series dataset included HRSV, HPIV, and HAdVs aggregate number of cases on a monthly, quarterly, and annual basis. This dataset was compiled from the Influenza-Like Illness (ILI) surveillance system's primary dataset. Data were collected independently based on the specific respiratory virus that caused the ILI and categorized per month, quarter, and year from 2007 to 2013. The Köppen-Geiger climate classification (1980-2016) at 1km resolution presented climatic features with high baseline resolution [328]. The regional map of the present Kenya climatic features was extracted from the global Köppen-Geiger climate classification system (1980-2016). The base map of Kenya administration boundaries and other geographical features were obtained from the humanitarian data exchange (HDX) open data library [347]. The dataset included the list of counties in Kenya with their respective surface and boundaries.

All datasets were recorded and managed in Microsoft Excel, Office Home and Student 2013. However, spatial data which required file formatting were managed in qGIS 3.10.3- A Coruña and SatScan version 9.6.1-Maryland. Also, other files including the raster data for climate features, and shapefile for administrative, surface and boundaries of Kenya were recorded with qGIS 3.10.3-A Coruña.

3.7. Data analysis

3.7.1. Eligibility criteria of published studies and unpublished reports

The eligibility criteria for the studies to be included in the systematic review and meta-analysis of prevalence were defined (Annex 6). The review considered studies that reported HRSV, HPIV, and HAdV infections confirmed by laboratory testing. The review also included studies that enrolled participants with a variety of syndromes, such as acute respiratory tract infections in

general, influenza-like illnesses (ILIs), severe acute respiratory illnesses (SARIs), and pneumonia. The studies which documented asymptomatic cases were excluded. Other inclusion criteria included age groups, study designs, publication language, and study period.

For studies that reported children, adults, or both, all age groups were considered. Furthermore, the review included observational studies with prospective and retrospective designs, as well as cross-sectional and cohort studies that were descriptive, analytical, or both. Individual case reports, case series, letters to editors, commentaries, and qualitative studies were all excluded. For both published and grey literature studies, the language of the search was limited to English. Inquiries about Burundi were directed to the ministry of health in both English and French. Only studies conducted between January 1st, 2007 and December 31st, 2020 were considered for inclusion in the review.

3.7.2. Search strategies

The search strategies were developed and tested first on the Medline database. This was accomplished through the use of keywords, Medical Subject Heading (MeSH) terminologies, and synonyms. The search strategies were also tailored to the Global Index Medicus database as well as grey literature (Annex 7). Data from published studies and unpublished reports that met the eligibility criteria for the systematic review were recorded, verified, and validated. The initial search was conducted by double-checking the text words contained in the title and abstract of the index terms, which were used to describe the articles using keywords and MeSH terminologies (Annex 8). In this way, a search strategy for sourcing published studies was developed to obtain studies in EAC partner states (Kenya, Tanzania, Uganda, Rwanda, Burundi a. Furthermore, all studies chosen for inclusion had their reference lists screened for additional publications. Unpublished study searches were carried out using databases from government medical research institutions, teaching hospitals, and university libraries in East African Community partner countries previously cited.

3.7.3. Citations management and data extraction

All citations identified were compiled and imported into the Zotero software (version 5.0), and duplicates were removed. Titles and abstracts were re-screened against the eligibility criteria, and studies meeting the criteria were retrieved in full and their details were imported into JBI SUMARI. Two parallel reviewers thoroughly assessed the full texts of selected studies against the eligibility criteria, with any disagreements resolved with a third investigator.

All selected studies were critically appraised for methodological quality. To accomplish this, two independent reviewers used the Joanna Briggs Institute's standardized critical appraisal instrument. This review followed the guidelines for systematic reviews of prevalence and incidence in the manual, and it used the JBI SUMARI software, which can be found at /www.jbisumari.org. Any disagreements that arose were resolved through discussion or with the assistance of a third reviewer, as previously stated.

The data extracted from selected studies were included in the review by two independent reviewers using a standardized data extraction tool in JBI SUMARI software. Specific information extracted from the data included the names of the primary authors, the year of publication, the locality, the age category, the length of the study period, the study design, the clinical condition, the specimen type, the laboratory test, the number of cases, and the total population. Age was classified as under-fives (<5 years old), fives and up (≥5 years old), or uncategorized age (all ages).

Clinical conditions were recorded as acute respiratory tract infections in studies that looked at both ILI and SARI (ARTIs). However, influenza-like illness (ILI) and severe acute respiratory illness (SARI) were considered in studies that specified the syndromes separately. Pneumonia was classified as a severe acute respiratory illness (SARI). The durations of the studies were divided into three categories: less than five months (5M), six to twelve months (6M-12M), and more than twelve months (>12M), indicating the short, medium, and long term, respectively. Microsoft Excel, Office Home and Student 2013 was used to organize the extracted data (Annex 9).

3.7.4. Risk of bias assessment

The risk of bias in the selected studies was assessed using an eight-variable rating scale [348–351]. Each study was given a score based on the number of variables that were well-defined and reported. The variables included: i) a study period of at least three months to allow laboratory processing of samples and analysis, ii) year of publication or documentation, iii) study area such as study location or a country, iv) age group description, v) clinical condition or syndrome with well-defined case definition, vi) standardized type of specimen collection, vii) laboratory methodology and viii) type of study design. Each variable was given a score of one (yes) for a well-defined record and a score of zero (no) for missing or unclear documentation. We summed each variable score that ranged from 0 to 8, with score categories ranging from high risk "0-2", medium risk "3-5", and low risk "6-8" for each study.

3.7.5. Data Synthesis

The studies that met the eligibility criteria were listed, and each variable of interest was extracted and imported from JBI SUMARI to Microsoft Excel for synthesis. The analysis was performed by using STATA®13 (StataCorp, College Station, TX). The dataset was reorganized and coded for analysis. Besides, the "Metaprop" package in the STATA program performed additional meta-analysis [352]. Initially, the crude numerators and denominators found in individual studies were used to calculate the unadjusted prevalence (p) of HRSV, HPIV, and HAdV infections (1).

$$p = \frac{n}{N} \times 100 \qquad (1)$$

Whereas, p is the crude prevalence, n the number of cases, and N population

The Freeman-Tukey double-arcsine transformation (2) technique was used with the metaprop command to ensure that studies with very low or high prevalence were included in the overall estimates [353]. This method stabilized the variance (3) of study-specific prevalence before using a random-effects model (RE) to generate a pooled prevalence estimate (4) and to assess heterogeneity [352]. The variance stabilizing transformation of proportions was given by:

$$t = \sin^{-1}\sqrt{\frac{n}{N+1}} + \sin^{-1}\sqrt{\frac{n+1}{N+1}} \quad (2)$$

Whereas n is the number of cases in the category, N is the number of population in the category. The variance *t* was given by:

$$Var(t) = \frac{1}{N+0.5} \quad (3)$$

The back transformation to proportions was performed by:

$$p = \frac{1}{2}\left\{1\ sgn(\cos t)\left[1 - \left(\sin t + \frac{\left(\sin t - \frac{1}{\sin t}\right)}{N}\right)^2\right]^{0.5}\right\} \quad (4)$$

Whereas "sgn" is the sign operator, N the population, and *t* the transformed value.

Given the observed heterogeneity between studies, the random-effects model allowed the effect to vary across studies, resulting in more conservative estimates with wider confidence intervals [354]. It was carried out using the method of DerSimonian and Laird [354,355], with 95% confidence intervals (CIs) estimated from exact binomial distribution (Clopper-Pearson) [356]. To assess heterogeneity, the I^2 statistic, Cochran's Q test, and subgroup analysis were used [357]. The variation of in-between studies differences was as expressed by I^2 statistical values' percentage, the interpretation was simplified with the "rule of thumb" [357–359]. A substantial heterogeneity was shown by the values of I^2 >50%, from the ranking categories of minimal (I^2< = 25%), low (I^2 = 25–49%), moderate (I^2 = 50–75%), and high (I^2> = 75%) [357,359].

To assess publication bias, an egger test was run using a meta-bias command [360]. The P<0.10 for the Egger test indicated a significant in between studies publication bias [361–363].

The prevalence of infection was defined for countries, age categories, and clinical illnesses. Besides, with a quantum geographical information system (qGIS), pie charts were generated to display HRSV, HPIV and HAdV prevalence of the infections in the region. The variables of public health importance were used to perform subgroup analysis. It included locality (Kenya, Tanzania, or Uganda), illnesses (ILI, SARI, or ARTIs), and age categories (below five, five and above, or all ages). The sensitivity analysis was accomplished using studies in Kenya, ARTIs, and below under five years' age category.

To conduct this review, the Joanna Briggs Institute's guidelines for systematic reviews of prevalence and incidence were followed. Besides, the report was written per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Annex 10). This review was registered under registration number CRD42018110186 in the International Prospective Register of Systematic Reviews (PROSPERO).

3.7.6. Morbidity burden estimate

The Influenza-like illness (ILI) dataset was reviewed for errors and participant characteristics were determined during an exploratory analysis. Further, a descriptive analysis was performed to determine the morbidity burden of HRSV, HPIV, and HAdVs infections (5). The morbidity burden of ILIs caused by HRSV, HPIV, and HAdVs was expressed as a proportion of laboratory-confirmed cases over the total ILI cases recorded during the surveillance period [364]. Also, HRSV, HPIV, and HAdVs proportion estimates were done for participant's demographic characteristics, clinical signs, surveillance sites, and the study period.

$$P = \frac{No.of\ laboratory-confirmed\ infection\ \ in\ the\ population\ at\ a\ specified\ time}{No.of\ total\ participants\ \ at\ that\ specified\ time} x100 \qquad (5)$$

Whereas, P is the proportion to express ILI morbidity burden

3.7.7. Seasonality assessment

The HRSV, HPIV, and HAdVs cases were organized in monthly time series data and analyzed to see if there was a seasonal pattern. A line plot was used to visualize the monthly cases from January 2007 to December 2013. To reduce noise, the number of cases was reorganized by an annual quartile and displayed as a line plot for each respiratory virus. The plot was smoothed further by applying the Discrete Fourier transformation (DFT) to the monthly time series data, as described by Bloomfield, 2000 [365]. The DFT technique (6) facilitated the identification of HRSV, HPIV, and HAdVs presence of clear seasonal patterns, if any.

$$d\,(f) = R(f)e^{i\emptyset(f)} \qquad (6)$$

Whereas, *R(f)* is the magnitude/amplitude (size of the epidemic) and Ø(*f*) the phase (timing of epidemic). It was anticipated 12 months (f_0= 1/12) of a cycle component. A 12-months moving average filter was done to extract the magnitude *R(f)* and the phase Ø(*f*) data (Annex 11).

Thereafter, to visualize seasonal patterns in the data for the study period (2007-2013), inverse discrete Fourier transformation (IDFT) was computed prior. The de-trended data were padded with zeros to increase the frequency of resolution [366]. The analysis was completed by use of Microsoft Excel-NumXL software add-in, while STATA®13 (STATA Corporation, College Station, TX, USA) was utilized to perform exploratory analysis.

3.7.8. Risk analysis

The outcome of HRSV, HPIV, HAdV presence(positive) or absence (negative) were verified for each participant with a number of identification in the ILI dataset. This dataset was organized and merged to participants' demographic determinants such as age, gender, occupation, origin, sick contact, school attendance, location/site, and year (illness onset). Climate (temperature, rainfall, and humidity), seasons (quarter-1, quarter-2, quarter-3, and quarter-4) and clinical characteristics were also joint determinants. Before measuring the difference in proportions with the chi-square test and exact 95% confidence intervals (CI) during exploratory analysis, the covariate categories were reviewed for obvious errors.

Furthermore, bivariate and multivariate logistic regression models (7) were used to measure the association between the outcome of interest (presence or absence) of each virus (HRSV, HPIV, and HAdVs) and covariates [340].

$$p = \frac{e^{(a+bx)}}{1+e^{(a+bx)}} \qquad (7)$$

Whereas, *p* is the conditional probability of experiencing an event given the predictors or covariates (x), constant intercept (a) and (b) the parameters to be estimated in the model.

The process of building and fitting all the logistic regression models was done with the logit package in the STATA®13 program. After adjusting for predictors, the odds ratios and probability value (p-value) were then reported for each virus outcome with a statistical significance level of $p<0.05$. This analysis was stratified by covariate categories to account for the confounding factors. The two-way interaction was assessed where necessary for predictors by adding a cross factor product (*) in the model or hashtag symbol (#). The lower Bayesian Information Criterion (BIC) indicated the best-fitted model [367].

3.7.9. Spatial-temporal analysis

The spatial datasets of HRSV, HPIV, and HAdV cases were separately explored and visualized to identify obvious errors. Besides, the base map of Kenya administration boundaries was verified in qGIS (V 3.10.3-A Coruña) for the country coordinate projection and counties labels. Thus, the base map was set together with the project coordinate projection (WGS84 UTM zone 37N/S). The HRSV, HPIV, and HAdV cases distribution were displayed per county. The symbology of colour categories was used to observe the pattern of a large to a small number of cases per county. A higher number of cases was represented by a darker colour, while a lower number of cases was represented by a lighter colour [368].

Kernel density estimation (KDE) was used to smooth the visualization by describing the spatial distribution of HRSV, HPIV, and HAdV cases in terms of hotspot identification in the study area. The Heat-map plugin in qGIS (V 3.10.3-A Coruña) created a density heat-map raster from a vector layer's input point. HRSV, HPIV, and HAdV case points density was calculated based on the number of case points in a location, which translated to the number of events per area unit. This enabled the identification of hotspots using a 10 km kernel radius (kernel bandwidth) [368,369]. However, the significant positive spatial autocorrelation cannot be determined using KDE.

Therefore, to detect significant positive spatial autocorrelation, a local Moran's I test (8) was applied on HRSV, HPIV, and HAdV cases aggregated data from the counties [368]. The indicators named “Local Indicators of Spatial Association (LISA)” were computed by:

$$I_i = Z_i \sum_{j,j\neq i}^{n} W_{ij} Z_J \qquad (8)$$

Where in a standardized form Z_i and Z_j were the observed values, and W_{ij} a spatial weights matrix in row-standardized format.

The hotspots analysis plugin in qGIS enabled to complete local Moran's I test with the use of queens ‘cases contiguity matrix and 999 random permutations and a statistical significance of 5% level [370]. LISA detected spatial clusters with values in quadrants defined as hot spots (high-high), cold spots (low-low), spatial outliers (high-low/low-high), and no significant local spatial autocorrelation [371–374]. On the other hand, LISA did not provide spatial cluster or hotspot characteristics.

Kulldorff's spatial scan statistic was used to account for various aspects of spatial pattern analysis and identify cluster characteristics. Various datasets were prepared in the format required by the SaTScan software (SatScan V9.6.1) to complete both analyses. A case file containing annual HRSV, HPIV, and HAdV cases per county from 2007 to 2013, a coordinate file containing the geographic coordinates of each county's centroid, and a population file containing the projected total population per county from 2007 to 2013 were gathered.

The analysis was based on the discrete Poisson model to identify purely spatial clusters of HRSV, HPIV, and HAdV cases by counties. On other hand, a space-time scan statistic was also used to determine the presence of space-time clusters of HRSV, HPIV, and HAdV cases per year during the study period. A Space-Time Poisson model was considered for the analysis of the study period of 2007-2013[368,375].

To identify clusters in space and space-time, the incidence of HRSV, HPIV, and HAdV was investigated retrospectively. SatSCan used a random process to search and test for a significantly increased risk of HRSV, HPIV, and HAdV cases exceeding the expected number within the specified spatial window [368,376]. The basic data used for the analysis were aggregated data per

county and each year of the study period (2007 to 2013). This represented the regions in Kenya that had cases identified via the surveillance program. The centroid coordinate of each county was extracted using the qGIS geometry tool from the geocoded location of the Kenya administrative boundaries vector layer. Using the centroids algorithm, a new point layer representing the centroids of Kenya counties was created. From 2007 to 2013, the features (latitude and longitude) were combined with annual HRSV, HPIV, and HAdV cases to the county centroid. This was done with qGIS and then formatted for further cluster analysis in SaTscan. In the SatScan, a cylindrical window with a circular geographic form based on each county centroid was used to identify clusters. The window moved across the study area in both space and time. The circular base of the cylinder represented a spatial dimension with a specified varying radius from 0 up to a maximum value. The cylinder height characterized the temporal dimension with a 1 year of time precision. The 50% maximum value was considered to represent the total population at risk in space and time. It was assumed that HRSV, HPIV, and HAdV cases were a Poisson distribution for each cylinder dimension. To evaluate the space and space-time clusters, it was assumed that cases were distributed randomly in space and space-time. The likelihood ratio for each cluster was calculated using the incidence of cases counted inside and outside the cylinder. The cylinder with the highest likelihood ratio was identified as a primary cluster. The likelihood ratio statistics and p-values were obtained using the 999 Monte Carlo randomizations test. This allowed significant space and space-time clusters to be identified with a statistical significance level of 5% [376].

To test the clusters' robustness, sensitivity analysis was performed with different maximum scanning window sizes ranging from 10% to 50% of the population at risk. Further, clusters were visualized in qGIS to obtain a map of cluster location in study regions and periods.

CHAPTER IV: THE RESULTS

4.1. The prevalence of Human Respiratory Syncytial Virus, Human Parainfluenza Virus, and Human Adenoviruses in the East Africa Community (2007-2020)

4.1.1. Systematic review records

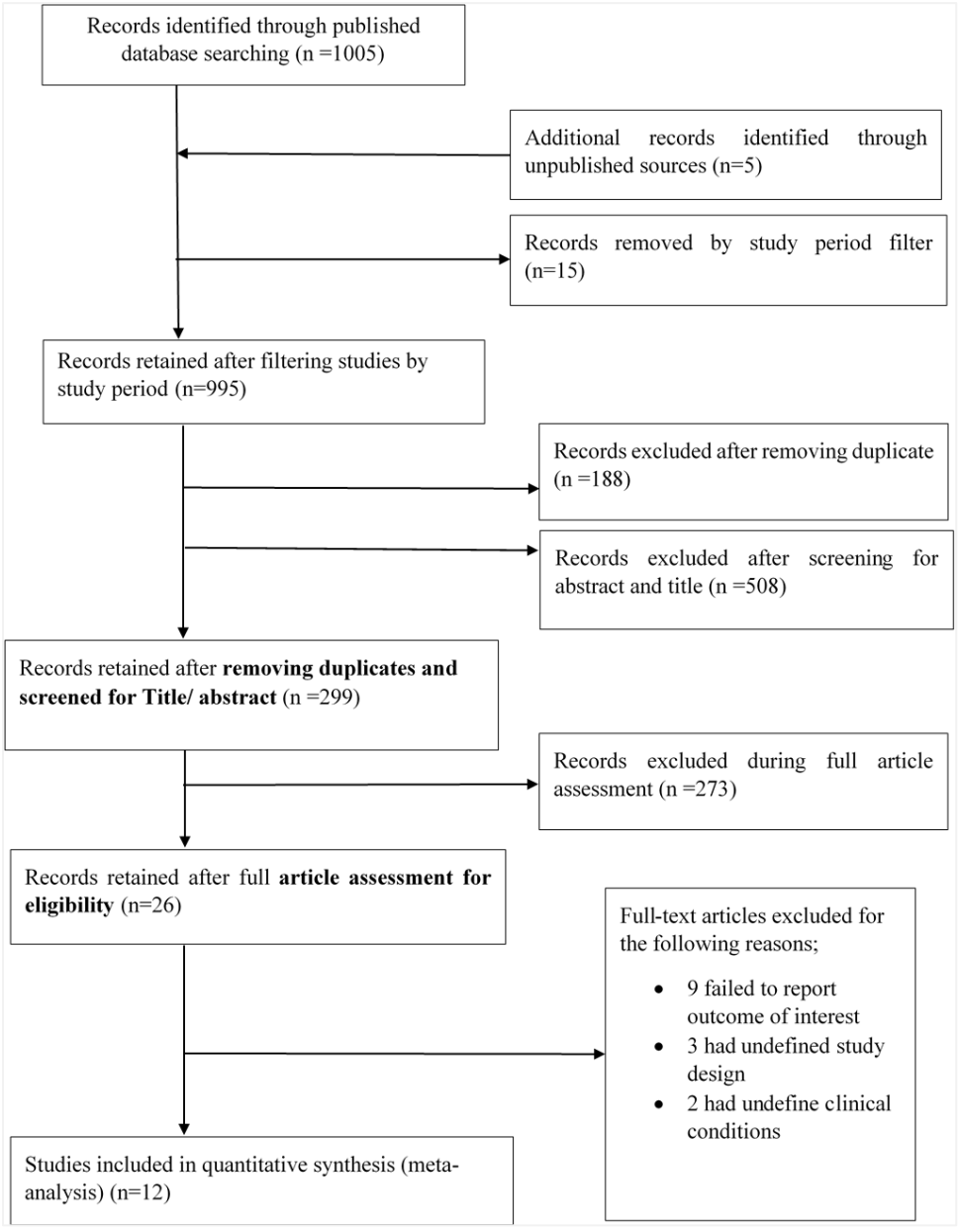
A systematic review of the literature found 1,005 published studies and 5 unpublished reports from grey literature (Fig 5). The review retained 995 studies from 2007 to 2020 using the period filter, with 990 having been published and 5 having been unpublished. After removing 188 duplicates, 807 were retained. Screening the abstracts and titles excluded a further 508 studies yielding 299 (of which 294 were published studies and 5 were unpublished). After screening for full articles, only 26 publications were left. However, among these, 9 studies failed to report the outcome of interest, 3 studies had undefined study designs, and 2 studies were missing critical information needed to define clinical conditions and were therefore excluded. Hence the quantitative synthesis (meta-analysis) retained a total of only 12 studies that met the eligibility criteria.

4.1.2. Characteristics of selected studies

The 12 eligible studies for the quantitative synthesis were published from 2009 to 2018 (Annex 12). Among those studies 10 reported HRSV, 8 HPIV, and 9 HAdV. Kenya had a large number of studies, including (n=8, 80%) for HRSV, (n=6, 75%) for HPIV and (n=7, 77.7%) of HAdV. Tanzania and Uganda each had one study that reported findings for all three respiratory viruses. There were no studies available for Rwanda, Burundi, or South Sudan during the review period. The majority of studies were cross-sectional by design and reported on the three respiratory viruses. Acute respiratory tract infections (ARTIs) were recorded in the majority of studies involving both ILI and SARI (n=6). ILI only was reported in a few studies (n=4). Furthermore, SARI was only reported in two studies (n=2). Individuals of all ages were enrolled in 5 studies, whereas participants under the age of five were only recruited in 4 studies. One study enrolled participants aged five years and older only. The majority of the studies (n=7) were conducted over a period of >12 months, while a few studies (n=2) were conducted over a short period of < 5 months and one study was conducted over a moderate period of 6-12 months.

The polymerase chain reaction was used as a diagnostic test in the majority of the studies (PCR). As specimens, oropharyngeal swabs (OPS) and nasopharyngeal swabs (NPS) were used. Most studies had a low risk of bias (Annex 13).

Figure 5. Review records



The meta-analysis included all studies that were designed to report the prevalence of the three viruses, HRSV, HPIV, and HAdV. However, not all of the studies reported evidence of infection with each of the three viruses.

Table 1. Study characteristics by respiratory viruses

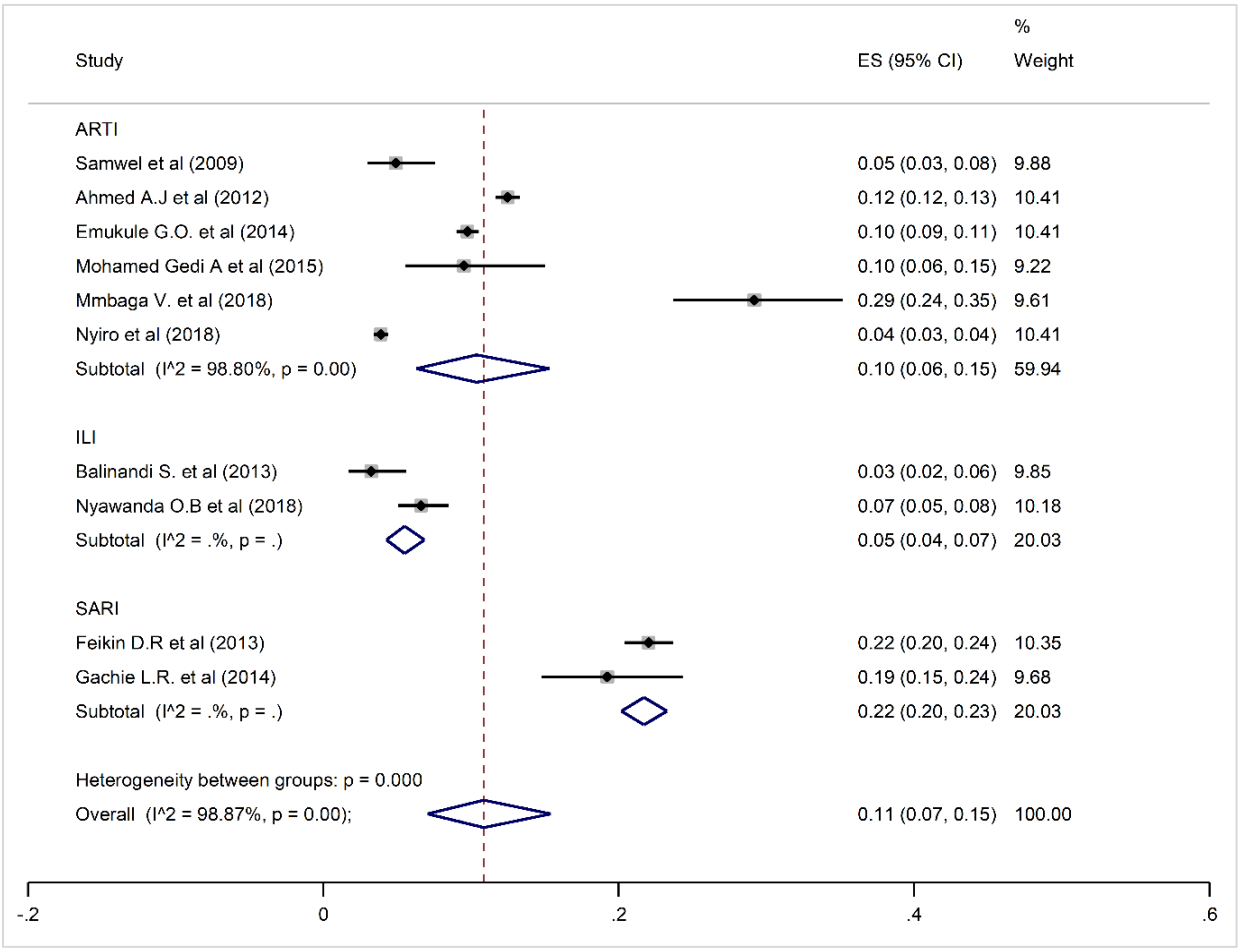
Outcomes	HRSV		HPIV		HAdV	
Study	**Number (n)**	**Proportion (%)**	**Number (n)**	**Proportion (%)**	**Number (n)**	**Proportion (%)**
Locality						
Kenya	8	80	6	75	7	77.7
Tanzania	1	10	1	12.5	1	11.1
Uganda	1	10	1	12.5	1	11.1
Clinical Condition						
ILI	2	20	2	25	2	22.2
SARI	2	20	1	62.5	2	22.2
ARTIs*	6	60	5	12.5	5	55.5
Population						
Under Five	3	30	1	12.5	2	22.2
Five and above	1	10	1	12.5	1	11.1
All ages**	5	50	4	50	5	55.5
Study design						
Cross-sectional	7	70	6	75	7	77.7
Cohort	2	20	1	12.5	1	11.1
Study Period						
Short-term (≤ months)	2	20	2	25	2	22.2
Medium-term (6-12 months)	1	10	1	12.5	1	11.1
Long-term (>12 months)	5	50	3	37.5	4	44.4
Lab Test						
Virus isolation	1	10	2	25	2	22.2
PCR	9	90	6	75	7	77.7
Specimens						
OPS	1	10	1	12.5	1	11.1
NPS	2	20	3	37.5	3	33.3
OPS and NPS	7	70	4	50	5	55.5
Risk of Bias						
Low risk	9	90	7	87.5	8	88.8
Moderate risk	1	10	1	12.5	1	11.1

*****ARTIs studies of both ILI and SARI. **All ages included uncategorized age groups. OPS=oropharyngeal swabs, NPS=nasopharyngeal swabs, PCR=polymerase chain reaction, ARTI=acute respiratory tract infection, ILI=influenza-like illness, SARI=severe acute respiratory illness, HRSV=human respiratory syncytial virus, HPIV=human parainfluenza virus, and HAdV=human adenovirus

4.1.3. Prevalence of Human Respiratory Syncytial Virus, Human Parainfluenza Virus and Human Adenoviruses

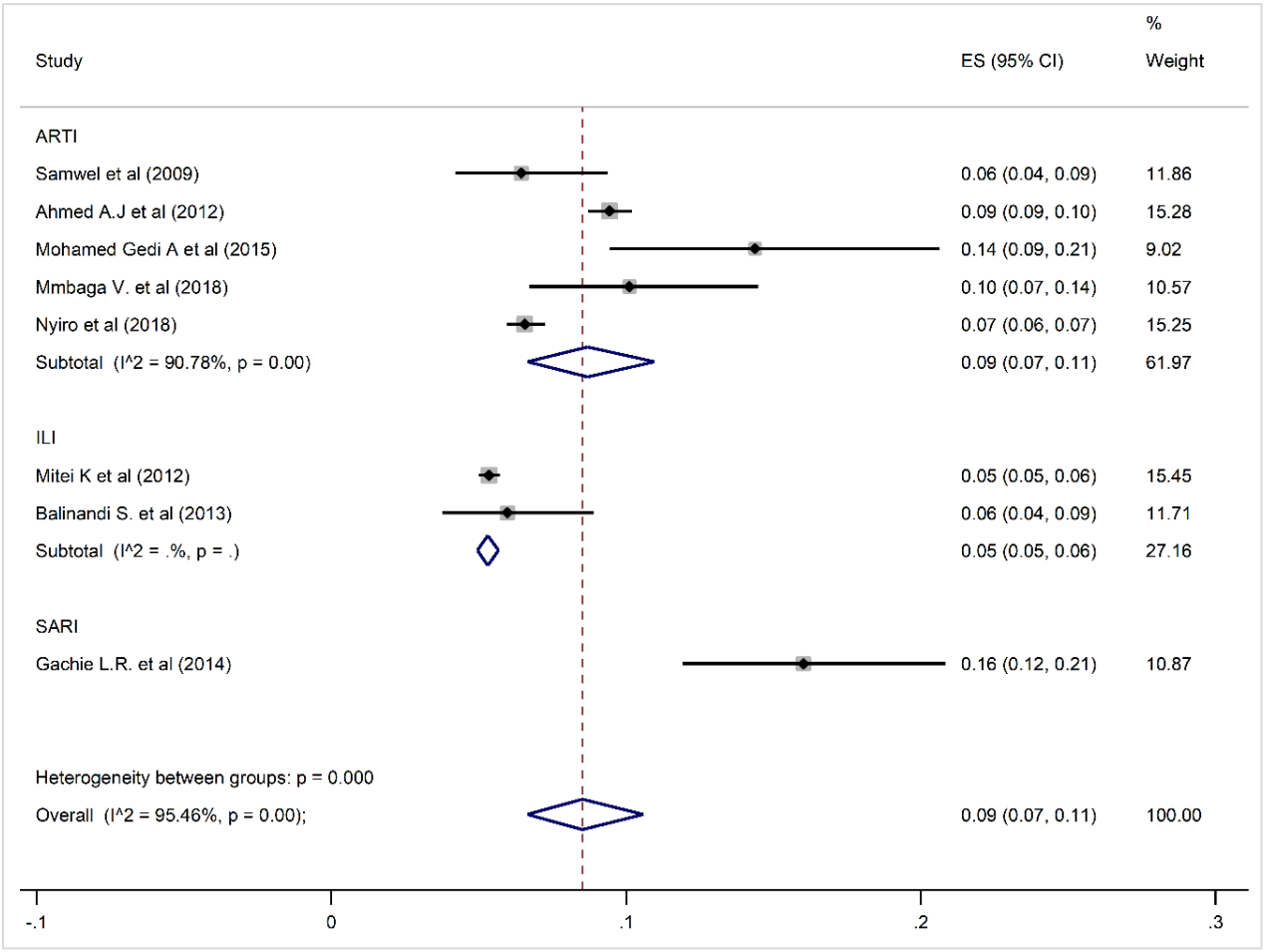
Based on data from 10 studies involving a total of 22,627 participants, the pooled prevalence of HRSV was 11% (95% CI: 7-15) in the general population (Fig 6). Furthermore, 18,619 people participated in 6 ARTIs studies, while 1,230 people participated in 2 ILI studies. There were only 2 SARI studies of 2,778 participants. Overall, inter-study heterogeneity was high, with I^2=98.8% and p<0.0001.

Figure 6. Pooled prevalence of HRSV in ARTIs, ILI, and SARI



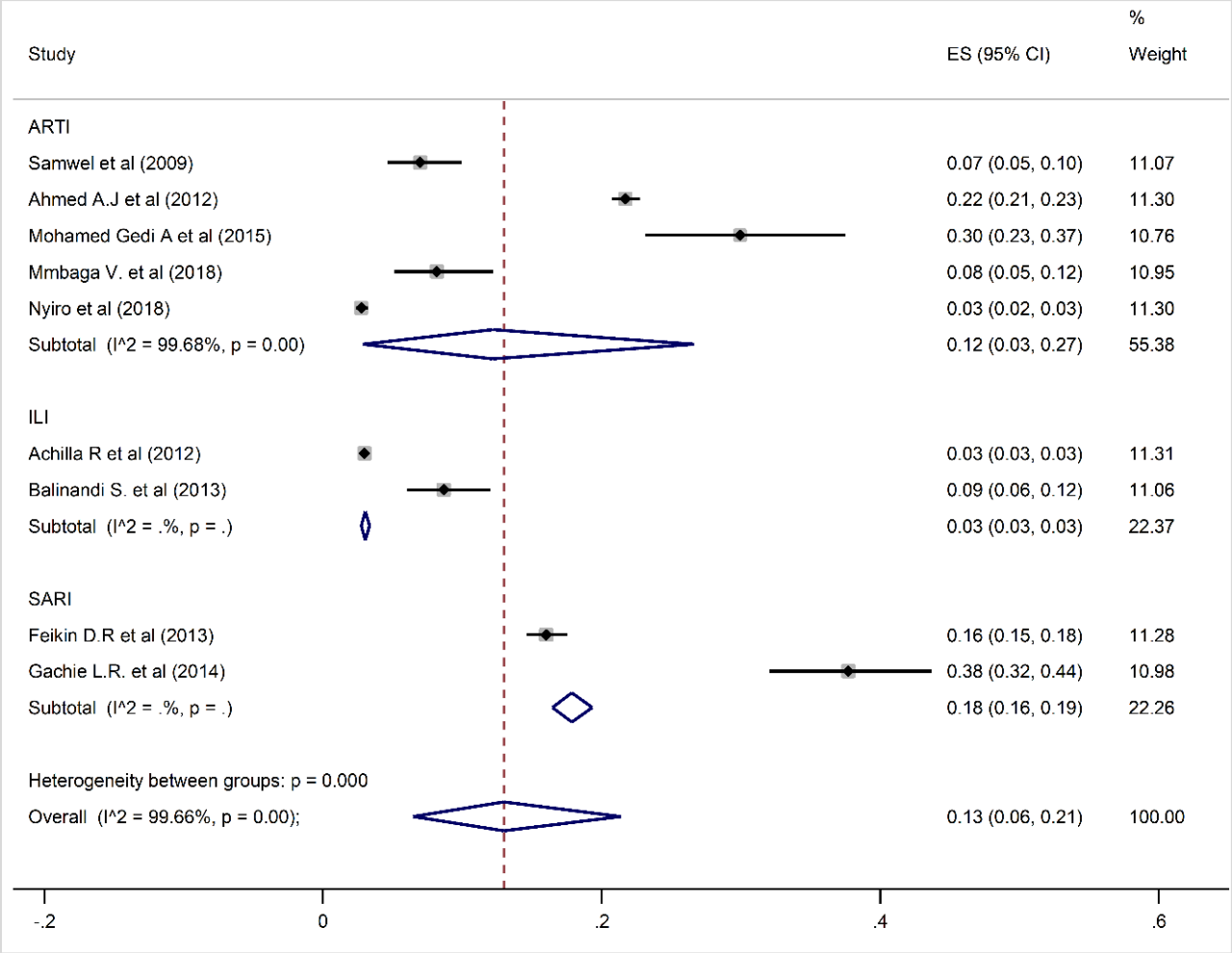
With a total of 28,363 participants from 8 studies, the pooled prevalence estimate for HPIV was 9% (95% CI: 7-11) (Fig 7). The total number of participants in the 5 ARTIs studies was 12,723 while the total number of participants in the 2 ILI studies was 15,359. In addition, 281 participants were recorded in 1 SARI study. All of the studies were found to have a high level of heterogeneity, with I^2=95.4% and p<0.0001.

Figure 7. Pooled prevalence of HPIV in ARTIs, ILI, and SARI



The pooled prevalence of HAdV was 13% (95 % CI: 6-21) in 9 studies, with a total of 28,829 participants (Fig 8). There were 5 ARTIs studies, with 12,723 participants, and 2 ILI studies, with 13,328 participants. In addition, 2,778 participants were enrolled in 2 SARI studies. The overall heterogeneity was high, with I^2=99.6% and p<0.0001 estimates.

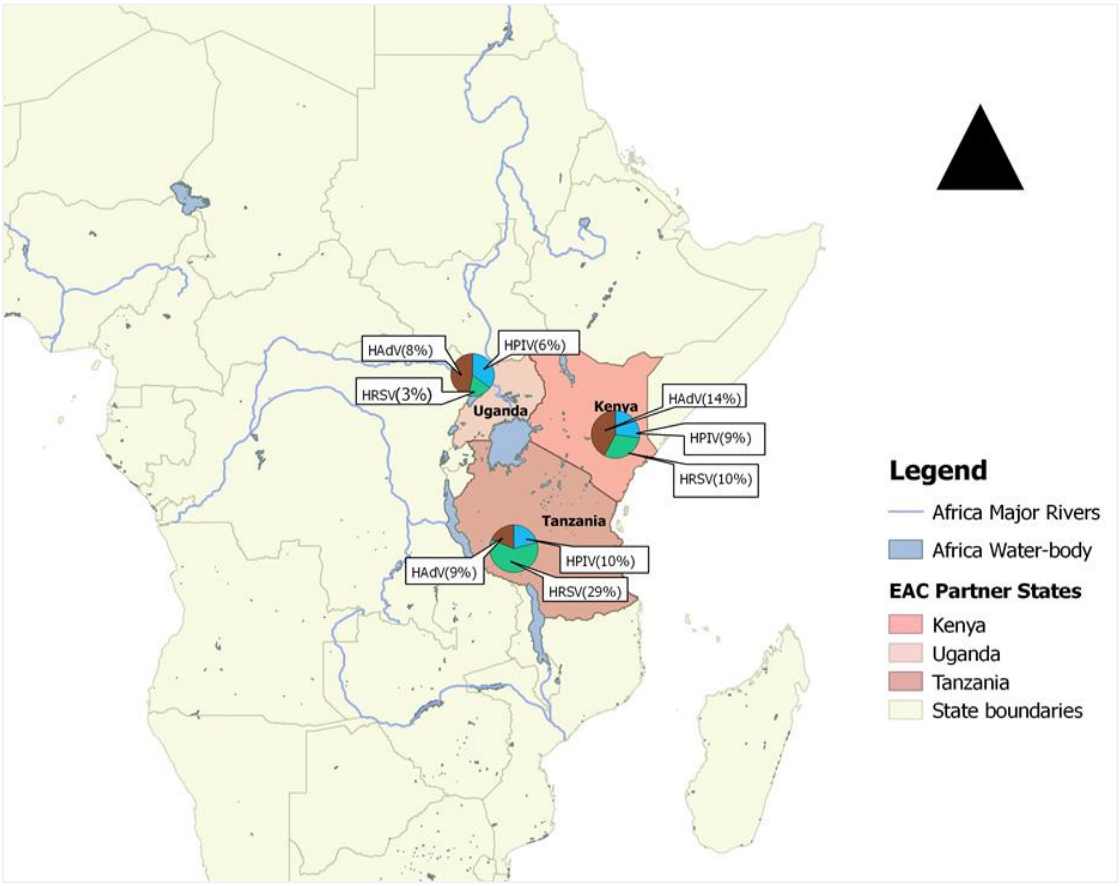
Figure 8. Pooled prevalence of HAdV in ARTIs, ILI, and SARI



When estimating the overall pooled prevalence for three viruses, significant heterogeneity was observed in the included studies. This was also observed for subgroup estimates based on syndromes, age groups, and locations (Table 2).

The distribution of the pooled prevalence for HRSV, HPIV and HAdV varied in EAC partner states with available data (Fig 9), syndromes and age groups.

Figure 9. Distribution of HRSV, HPIV and HAdV in three EAC partner states between 2007 and 2020



The prevalence of HRSV, HPIV and HAdV from pooled studies in Kenya were 10% (95% CI: 6-15), 9% (95% CI: 7-11) and 14% (95% CI: 7-25) respectively. For Tanzania, the pooled prevalence for HRSV was 29 % (95 % CI: 24-35), whereas HAdV and HPIV prevalence were 9% (95% CI: 6-12) and 10 % (95 % CI: 7-14), respectively. In Uganda, the pooled prevalence of HRSV, HPIV, and HAdV was 3% (95% CI: 2-6), 6% (95 %CI: 4-9), and 8% (95 %CI: 5-12), respectively. When the ARTIs was investigated for the studies, a pooled prevalence of 10% (6-15; 95% CI) was found for HRSV, 9% (7-11; 95% CI) for HPIV, and 12% (3-27; 95% CI) for HAdV. HRSV, HPIV, and HAdV pooled prevalence estimates from ILI studies were 5% (95 % CI: 4-7), 5% (95 % CI: 5-6), and 3% (95 % CI: 3-3.5), respectively. On the other hand, the estimates from

SARI studies were 22% (95 % CI: 20-23) for HRSV, 16% (95 % CI: 12-21) for HPIV, and 18% (95 % CI: 16-19) for HAdV.

HRSV, HPIV, and HAdV had an estimated prevalence of 9 % (95 % CI: 5-14), 9 % (95 % CI: 6-12), and 12 % (95 % CI: 4-24) respectively in studies that included participants of all ages. HRSV pooled prevalence was 10% (95 % CI: 2-24), HPIV was 6% (95 % CI: 4-9), and HAdV was 15% (95 % CI: 13-16) in studies that only enrolled children under the age of five. HRSV pooled prevalence was similar in the studies that enrolled people aged five years and above only, at 10% (95 %CI: 6-15), whereas HPIV and HAdV prevalence were at 14% (95% CI: 9-21) and 30% (95 % CI: 23-37), respectively.

Summary statistics of HRSV (Table 2), HPIV (Table 3), and HAdV (Table 4) including Egger's test indicated no evidence of publication bias. While significant heterogeneity was observed in both the overall and in subgroup analysis, no publication bias was detected in subgroup analyses that had enough studies (ARTIs, All ages, and Kenya) to assess sensitivity. When performing sensitivity analysis on ARTI studies, similar prevalence to the overall prevalence was observed: 12 % (95 % CI: 3-27) for HAdV, 10 % (95 % CI: 6-15) for HRSV, and 9% (95% CI: 7-11) for HPIV. Furthermore, studies involving people of all ages found a pooled prevalence for HAdV of 12% (95 % CI: 4-24), HRSV of 9% (95 % CI: 5-14), and 9% (95 % CI: 6-12) for HPIV. In Kenya, the prevalence of HAdV, HRSV, and HPIV was reported to be 14 % (95% CI: 7-25), 10 % (95 % CI: 6-15), and 9 % (95 % CI: 7-11), respectively.

Table 2.Summary statistics of human respiratory syncytial virus' prevalence

Outcome	**HRSV**							
Groups	**Studies (n)**	**Cases (n)**	**Pop (N)**	**Crude Prev. (95%CI)**	**Pooled Prev. (95%CI)**	**I^2 (%)**	**P-value (Egger)**	**P-value (hetero-geneity)**
Overall	10	2358	22627	10 (10-11)	11 (7-15)	98.87	0.618	**<0.0001**
Syndromes								
ARTIs	6	1685	18619	9 (8-9)	10 (6-15)	98.8	0.654	**<0.0001**
ILI	2	69	1230	5 (4-7)	5 (4-7)	-	-	**-**
SARI	2	604	2778	22 (20-23)	22 (20-23)	-	-	**-**
Age								
All age	5	1641	18456	9 (8-9)	9 (5-14)	98.94	0.914	**<0.0001**
Under Five	3	626	3746	16 (15-18)	10 (2-24)	-	-	**-**
Five and above	1	16	168	9 (5-15)	10 (6-15)	-	-	**-**
Locality								
Kenya	8	2271	22001	10 (10-11)	10 (6-15)	99	0.763	**<0.0001**
Tanzania	1	75	257	29 (23-35)	29 (24-35)	-	-	**-**
Uganda	1	12	369	3 (1-5)	3 (2-6)	-	-	**-**

N: population, prev.: prevalence, CI: confidence interval, I^2 (index value): the variation in effect sizes attributable to heterogeneity, P: probability value, ARTI=acute respiratory tract infection, ILI=influenza-like illness, SARI=severe acute respiratory illness, HRSV=human respiratory syncytial virus

Table 3. Summary statistics of human parainfluenza virus' prevalence

Outcome					**HPIV**			
Groups	**Studies (n)**	**Cases (n)**	**Pop (N)**	**Crude Prev. (95%CI)**	**Pooled Prev. (95%CI)**	**I^2 (%)**	**P-value (Egger)**	**P-value (hetero-geneity)**
Overall	8	1905	28363	7 (6-7)	9 (7-11)	95.4	0.179	**<0.0001**
Syndromes								
ARTIs	5	1037	12723	8 (7-8)	9 (7-11)	90.7	0.681	**<0.0001**
ILI	2	823	15359	5	5 (5-6)	-	-	**-**
SARI	1	45	281	16 (12-20)	16 (12-21)	-	-	**-**
Age								
All age	4	1029	12561	8 (8-9)	9 (6-12)	94.3	0.706	**<0.0001**
Under five	1	25	388	6 (4-9)	6 (4-9)	-	-	**-**
Five and above	1	24	167	14 (9-21)	14 (9-21)	-	-	**-**
Locality								
Kenya	6	1857	27737	6 (6-7)	9 (7-11)	96.6	0.205	**<0.0001**
Tanzania	1	26	257	10 (7-14)	10 (7-14)	-	-	**-**
Uganda	1	22	369	6 (4-9	6 (4-9)	-	-	**-**

N: population, prev.: prevalence, CI: confidence interval, I^2 (index value): the variation in effect sizes attributable to heterogeneity, P: probability value, ARTI=acute respiratory tract infection, ILI=influenza-like illness, SARI=severe acute respiratory illness, HPIV=human parainfluenza virus

Table 4. Summary statistics of human adenoviruses' prevalence

Outcome	**HAdV**							
Groups	**Studies (n)**	**Cases (n)**	**Pop (N)**	**Crude Prev. (95%CI)**	**Pooled Prev. (95%CI)**	**I^2 (%)**	**P-value (Egger)**	**P-value (hetero-geneity)**
Overall	9	2537	28829	9 (8-9)	13 (6-21)	99.66	0.337	**<0.0001**
Syndromes								
ARTIs	5	1614	12723	13 (12-13)	12 (3-27)	99.68	0.994	**<0.0001**
ILI	2	417	13328	3	3 (3-3.5)	-	-	**-**
SARI	2	506	2778	18 (17-20)	18 (16-19)	-	-	**-**
Age								
All age	5	2039	25520	8 (7-8)	12 (4-24)	99.8	0.516	**<0.0001**
Under Five	2	427	2885	15 (13-16)	15 (13-16)	-	-	**-**
Five and above	1	50	167	30 (23-37)	30 (23-37)	-	-	**-**
Locality								
Kenya	7	2484	28203	9 (8-9)	14 (7-25)	99.74	0.307	**<0.0001**
Tanzania	1	21	257	8 (5-12)	8 (5-12)	-	-	**-**
Uganda	1	32	369	9 (6-12)	9 (6-12)	-	-	**-**

N: population, prev.: prevalence, CI: confidence interval, I^2 (index value): the variation in effect sizes attributable to heterogeneity, P: probability value, ARTI=acute respiratory tract infection, ILI=influenza-like illness, SARI=severe acute respiratory illness, HAdV=human adenovirus

4.2. Morbidity burden of ILI, Seasonality, and Factors Associated with the Human Respiratory Syncytial Virus, Human Parainfluenza Virus, and Human Adenovirus Infections in Kenya (2007-2013)

For the study period of January 2007 to December 2013, the ILI surveillance program recruited 17,261 participants from the eight surveillance sites. HRSV and HAdVs were not subtyped in this study, and only the three subtypes of HPIV 1-3 had laboratory subtype data. The sites with a high proportion of participants included (17%) Kisii, (17%) New Nyanza and (16%) Mbagathi (Table 5). Port Reitz enrolled a lower number of study participants (12%). Besides, Kericho and Alupe had (11%) each, while Malindi and Isiolo had (10%) each of the study participants. HRSV- caused morbidity burden of influenza-like illness was 3.1% (2.8-3.3; 95% CI) in overall. Besides, 5.3% (5.0-5.6; 95% CI) was caused by HPIV and 3.3% (3.1-3.6, 95% CI) by HAdV. The most dominant HPIV types was (38.6 %) HPIV-3 and (34.1 %) HPIV-1, whereas HPIV-2 was only (10.4%). Multiple HPIV coinfections accounted for 16.8 % of all HPIV cases.

The proportions of ILI caused by HRSV, HPIV, and HAdV varied demographically (Table 5). HRSV-caused ILI differed significantly across the age groups ($p<0.001$), as were the ILIs due to HPIV and HAdV. In addition, differences in the proportions for HRSV ($p=0.023$), HPIV ($p=0.001$), and HAdV ($p=0.012$) were observed among occupation categories. For HRSV, HPIV, and HAdV infections, there was a significant difference in the proportion of participants who attended school ($p<0.001$) compared to non-school attending participants.

The proportion of ILI caused by HRSV, HPIV, and HAdV varied significantly across surveillance sites and over the course of the surveillance period. Infections with HRSV, HPIV, and HAdV were found at all surveillance sites, with varying distributions. HRSV infections were found high in Malindi (5%), Port-Reitz (4%), and Kisii (4%). Nevertheless, other surveillance sites had lower proportions of HRSV infections. Malindi, Port-Reitz, Kisii, Kericho, and Isiolo had high proportions of HPIV infections whereas HAdV infections were found to be high in Malindi (5%), New-Nyanza (4%) and Mbagathi (4%).

Table 5. Demographic characteristics of study participants by respiratory viruses

Variable/ Outcome		HRSV			HPIV			HAdVs		
Overall	**Total Population**	**Positive**	**Negative**	**Chi-square**	**Positive**	**Negative**	**Chi-square**	**Positive**	**Negative**	**Chi-square**
	N (%)	n (%)	n (%)	P-value	n (%)	n (%)	P-value	n (%)	n (%)	P-value
	17261	539 (3)	16722 (97)		922(5)	16339(95)		581(3)	16680(97)	
Gender				**0.429**			**0.471**			**0.106**
Male	8998(52)	290(3)	8708(97)		470(5)	8528(95)		322(4)	8676(96)	
Female	8263(48)	249(3)	8014(97)		452(5)	7811(94)		259(3)	8004(97)	
Age				**<0.001**			**<0.001**			**<0.001**
≤1year	9650(56)	351(4)	9299(96)		557(6)	9093(94)		391(4)	9259(96)	
2 to 4 years	6139(35)	166(3)	5973(97)		327(5)	5812(95)		175(3)	5964(97)	
5 to ≤ 18years	1163(7)	20(2)	1143(98)		32(3)	1131(97)		14(1)	1149(99)	
19-49 years	300(2)	2(0.6)	298(99)		6(2)	294(98)		1(0.3)	299(99)	
50+ years	9(0.05)	0(0)	9(100)		0(0)	9(100)		0(0)	9(100)	
Occupation				**0.023**			**0.001**			**0.012**
Children	16482(95)	528(3)	15954(97)		905(5)	15577(95)		567(3)	15915(97)	
Students	420(2)	9(2)	411(98)		11(3)	409(97)		13(3)	407(97)	
Others	355(2)	2(0.5)	353(99)		6(2)	349(98)		1(0.2)	354(99)	
Origin				**0.335**			**0.458**			**0.241**
Urban	16932(98)	532(3)	16400(7)		902(5)	16030(95)		574(3)	16358(97)	
Rural	319(2)	7(2)	312(98)		20(6)	299(94)		7(2)	312(98)	
Sick contact				**0.213**			**0.362**			**0.368**
Yes	6001(35)	174(3)	5827(97)		308(5)	5693(95)		192(3)	5809(97)	
No	11245(65)	365(3)	10880(97)		614(5)	10631(95)		389(3)	10856(97)	
Attend school				**<0.001**			**<0.001**			**<0.001**
Yes	3191(18)	60(2)	3131(98)		123(4)	3068(96)		60(2)	3131(98)	
No	14052(81)	479(3)	13573(97)		798(6)	13254(94)		521(4)	13531(96)	

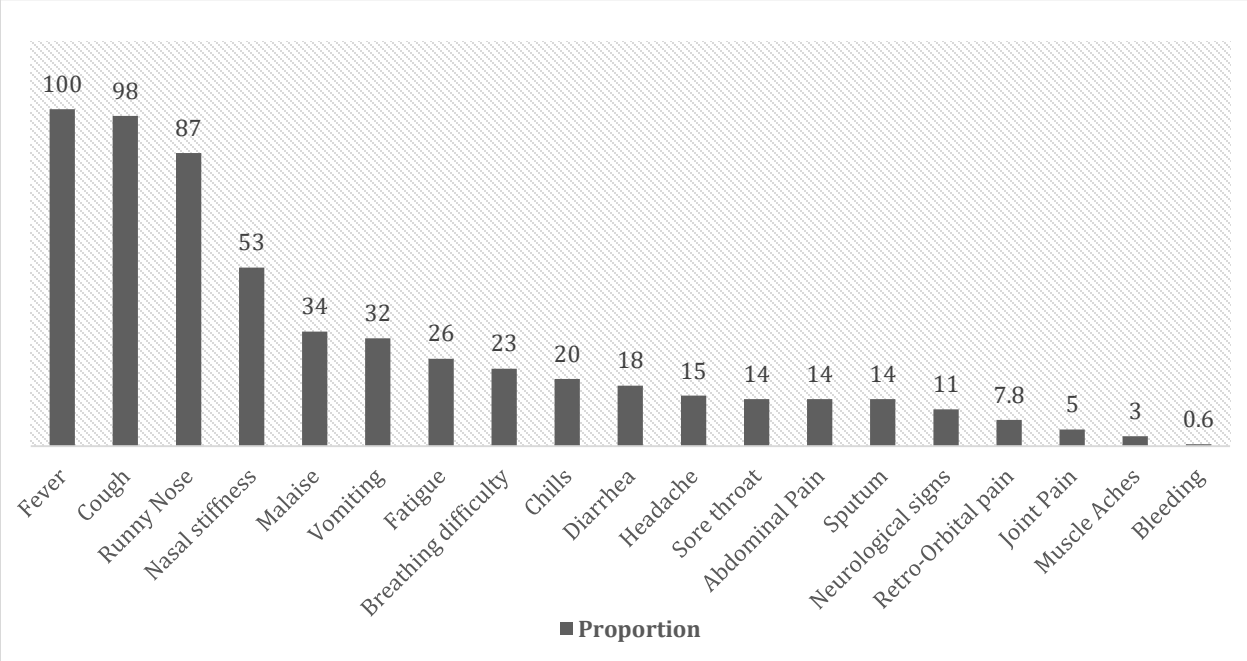
Table 5. Demographic characteristics of study participants by respiratory viruses

Variable/ Outcome		HRSV			HPIV			HAdVs		
Location*				**<0.001**			**0.002**			**<0.001**
Alupe	1884(11)	30(2)	1854(98)		75(4)	1809(96)		30(2)	1854(98)	
Isiolo	1347(8)	44(3)	1303(97)		79(6)	1268(94)		33(2)	1314(98)	
Kericho	1996(11)	64(3)	1932(97)		127(6)	1869(94)		65(3)	1931(97)	
Kisii	2950(17)	128(4)	2822(96)		177(6)	2773(94)		94(3)	2856(97)	
Malindi	1327(7)	62(5)	1265(95)		80(6)	1247(94)		68(5)	1259(95)	
Mbagathi	2810(16)	46(2)	2764(98)		125(4)	2685(96)		117(4)	2693(96)	
New Nyanza	2938(17)	79(3)	2859(97)		142(5)	2796(95)		108(4)	2830(96)	
Port Reitz	2009(12)	86(4)	1923(96)		117(6)	1892(94)		66(3)	1943(97)	
Year				**<0.001**			**<0.001**			**<0.001**
2007	2925(17)	22(1)	2903(99)		82(3)	2843(97)		133(5)	2792(95)	
2008	3052(18)	103(4)	2949(96)		185(6)	2867(94)		101(3)	2951(97)	
2009	3806(22)	86(2)	3720(98)		123(3)	3683(97)		131(3)	3675(97)	
2010	3027(17)	116(4)	2911(96)		188(6)	2839(94)		102(3)	2925(97)	
2011	2289(13)	140(6)	2149(94)		138(8)	2151(94)		44(2)	2245(98)	
2012	1338(8)	53(4)	1285(96)		110(8)	1228(92)		52(4)	1286(96)	
2013	824(5)	19(2)	805(98)		96(12)	728(88)		18(2)	806(98)	

*ILI surveillance sites location

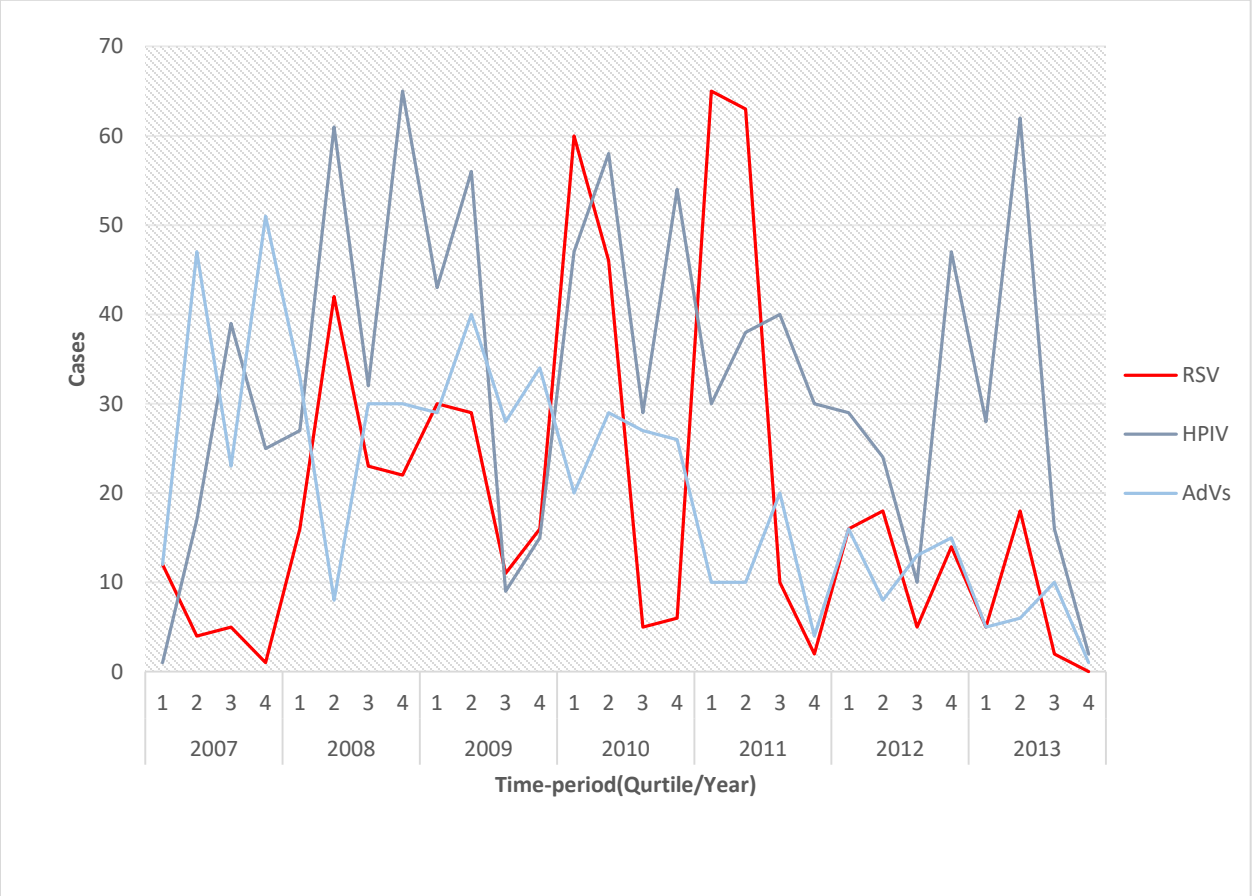
The participants' enrolled in the ILI surveillance system presented with several clinical signs (Fig 10). Among the most common symptoms were fever (100%), cough (98%), runny nose (87%), and nasal stuffiness (53%). Other clinical characteristics including difficulty in breathing, malaise, fatigue, muscle aches, diarrhoea, headache, vomiting, sore throat, sputum production, abdominal pain, joint pain, retro-orbital pain, bleeding, and neurological signs were counted in less than (35%) of the ILI participants. HRSV, HPIV, and HAdV infections caused various symptoms of which the proportion was specific to the virus type (Annex 14). After adjusting for age, none of the clinical characteristics, except for fever and cough, were significantly associated with HRSV, HPIV, and HAdV among the participants (Annex 15).

Figure 10. Proportion of participant's clinical characteristics



In a quarterly pattern, HRSV, HPIV, and HAdV circulated throughout the 7-year surveillance period from 2007 to 2013 (Fig 11). HRSV activity had three major peaks following the years 2008, 2010, and 2011. HPIV was the most dominant of the three respiratory viruses, with spikes of HPIV cases occurring irregularly throughout the surveillance period. On other hand, HAdVs had two major erratic spikes observed in 2007 and 2009, and the number of cases decreased gradually toward 2013.

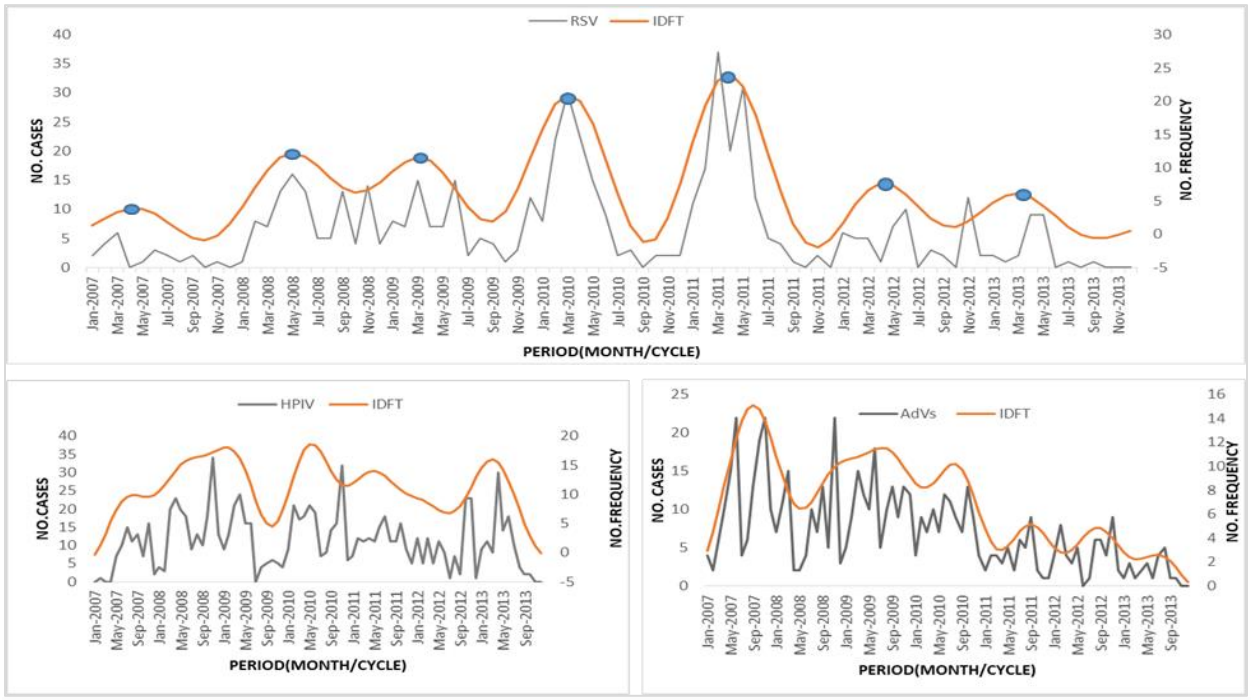
Figure 11. Quartile trend of the HRSV, HPIV, and HAdV during the study period



* Quarterly trend of Influenza-like illness (ILI) by HRSV, HPIV, and HAdVs, Kenya (2007-2013). Human respiratory syncytial virus (HRSV), human parainfluenza virus (HPIV), and human adenoviruses (HAdVs).

HRSV seasonal peak was well defined and appeared in April-May each year of the surveillance period (Fig 12). The seasonal trends of HPIV and HAdV cases revealed no clear pattern through the Fourier series analysis.

Figure 12. The monthly trend of the HRSV, HPIV, and HAdV during the study period



*Monthly trend of Influenza-like illness (ILI) by HRSV, HPIV, and HAdVs, Kenya (2007-2013). Human respiratory syncytial virus (HRSV), human parainfluenza virus (HPIV), and human adenoviruses (HAdVs). The inverse discrete Fourier transform (IDFT) represents the monthly periodicity trend for every 12 months cycle. Blue dots denote the observed seasonal peak of HRSV around April-May.

HRSV, HPIV, and HAdV infections were significantly associated with factors including demographics, season, and climate (Table 6). The proportions of all three respiratory viruses were higher in Infants than in other age groups. Furthermore, HRSV was more likely to occur (OR: 2.73) in the Jan-March quarter (Q1) and the Apr-Jun quarter (Q2) (OR: 3.01) than in the Oct-Dec quarter (Q4). HRSV infections were more likely to occur in hot land surface temperature (≥40°C) than cooler land surface temperature (<30°C) (OR: 2.75). Besides, HRSV infections were more likely to occur (OR: 1.68) in the warmer air temperature range (19-22.9°C) than in cooler air temperature (<19°C), and more likely (OR=1.32) in moderate rainfall (150-200mm) compared to low rainfall (<150mm).

Both HPIV and HAdV infections were not associated with either season or climatic conditions. However, HAdV infections were more likely (OR=2.25) to occur in higher land surface temperature (≥40°C) compared to cooler land surface temperature (<30°C).

Table 6. Factors associated with the human respiratory syncytial virus, human parainfluenza virus, and human adenoviruses

Variable/Outcome	HRSV				HPIV				HAdVs			
	Crude OR* (95% CI)	P-Value	Adjusted OR* (95%CI)	P-Value	Crude OR* (95% CI)	P-Value	Adjusted OR* (95%CI)	P-Value	Crude OR* (95% CI)	P-Value	Adjusted OR* (95%CI)	P-Value
Age		**<0.001**				**<0.001**				**<0.001**		
≤1year	Ref		Ref		Ref		Ref		Ref		Ref	
2 to 4 year	0.73(0.61-.088)	0.001	0.75(0.62-0.91)	0.003	0.91(0.79-1.05)	0.235	0.90(0.78-1.03)	0.153	0.69(0.57-0.83)	<0.001	0.69(0.58-0.83)	<0.001
5 to ≤ 18year	0.46(0.29-0.73)	0.001	0.50(0.31-0.79)	0.003	0.46(0.32-0.66)	<0.001	0.45(0.31-0.66)	<0.001	0.28(0.16-0.49)	<0.001	0.29(0.17-0.49)	<0.001
19-49 year	0.17(0.04-0.71)	0.015	0.19(0.04-0.77)	0.02	0.33(0.14-0.75)	0.008	0.33(0.14-0.76)	0.009	0.07(0.01-0.56)	0.011	0.08(0.01-0.59)	0.013
50+ year	NA											
Quartile		**<0.001**				**<0.001**				**0.0082**		
Oct-Dec(Q4)	Ref		Ref		Ref		Ref		Ref		Ref	
Jan-March(Q1)	3.10(2.32-4.14)		2.73(2.00-3.73)	<0.001	0.77(0.63-0.93)		0.83(0.68-1.02)	0.091	0.69(0.54-0.88)		0.62(0.47-0.80)	<0.001
Apr-Jun(Q2)	2.98(2.23-3.97)		3.01(2.23-4.07)	<0.001	1.07(0.90-1.28)		1.07(0.90-1.27)	0.432	0.74(0.58-0.93)		0.81(0.63-1.04)	0.101
Jul-Sept(Q3)	0.94(0.66-1.35)		1.05(0.73-1.52)	0.768	0.69(0.56-0.84)		0.71(0.58-0.87)	0.001	0.90(0.71-1.13)		0.87(0.69-1.11)	0.28

*Q1: quarter one; *Q2: quarter two; *Q3: quarter three; *Q4: quarter four

Table 6. Factors associated with the human respiratory syncytial virus, human parainfluenza, and human adenoviruses

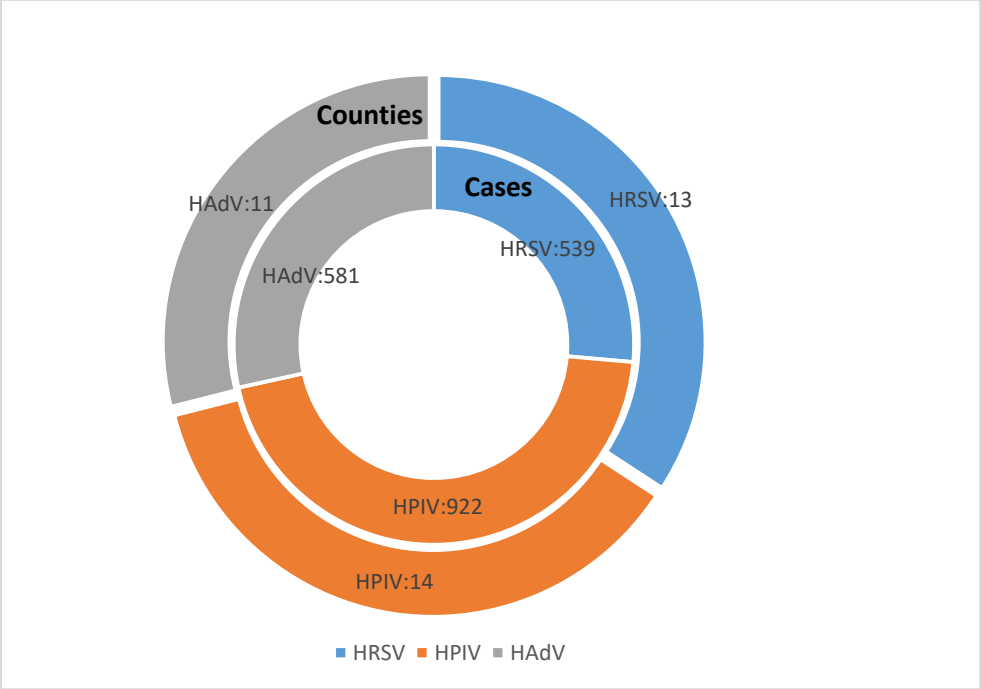
Variable/Outcome	HRSV				HPIV				HAdVs			
	Crude OR* (95% CI)	P-Value	Adjusted OR* (95%CI)	P-Value	Crude OR* (95% CI)	P-Value	Adjusted OR* (95%CI)	P-Value	Crude OR* (95% CI)	P-Value	Adjusted OR* (95%CI)	P-Value
LTM LST*		**<0.001**				**0.0048**				**0.0032**		
Cooler(<30°C)	Ref		Ref		Ref		Ref		Ref		Ref	
Warmer(30-39.9°C)	1.05(0.87-1.25)		0.93(0.75-1.15)	0.529	0.85(0.74-0.98)		0.90(0.78-1.05)	0.199	0.96(0.80-1.14)		1.02(0.85-1.23)	0.775
Hot(≥40°C)	3.42(2.44-4.78)		2.75(1.79-4.23)	<0.001	0.51(0.29-0.87)		0.56(0.32-0.97)	0.041	2.00(1.36-2.95)		2.25(1.48-3.43)	<0.001
MM AT*		**0.0001**				**0.5487**				**0.7885**		
Cooler(<19°C)	Ref		Ref		Ref				Ref			
Warmer(19-22.9°C)	2.23(1.38-3.60)		1.68(1.03-2.76)	0.037	1.15(0.88-1.51)				1.06(0.76-1.47)			
Hot(≥23°C)	2.59(1.58-4.23)		1.61(0.95-2.73)	0.072	1.11(0.83-1.49)				0.99(0.70-1.41)			
LTM rainfall*		**<0.001**				**0.3126**				**0.0337**		
Low (<150mm)	Ref		Ref		Ref				Ref		Ref	
Moderate(150-200mm)	1.62(1.30-2.01)		1.32(1.05-1.66)	0.016	1.08(0.89-1.30)				0.86(0.67-1.11)		0.93(0.72-1.21)	0.627
Heavy(>200mm)	1.67(1.25-2.22)		1.04(0.75-1.44)	0.781	1.19(0.93-1.52)				0.63(0.43-0.93)		0.66(0.43-1.00)	0.055

* LTM LST: Long term mean land surface temperature; * MMAT: monthly mean air temperature; * LTM rainfall: long term mean rainfall; *Q1: quarter one; *Q2: quarter two; *Q3: quarter three; *Q4: quarter four

4.3. The Spatial and Spatio-temporal Distributions of Human Respiratory Syncytial Virus, Human Parainfluenza Virus, and Human Adenoviruses in Kenya (2007-2013)

HRSV was reported in 13 counties (n=539) during the surveillance period of 2007-2013. Furthermore, HPIV and HAdV were described in 14 counties (n=922) and 11 counties (n=581), respectively (Fig 13).

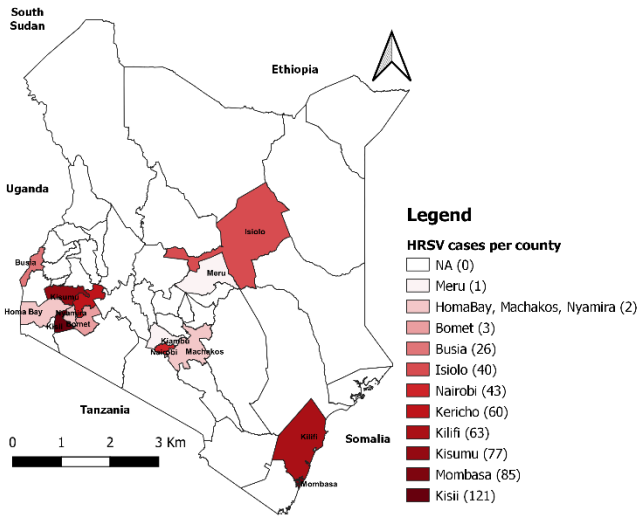
Figure 13. Summary statistics of HRSV, HPIV, and HAdVs cases and counties in Kenya (2007-2013)



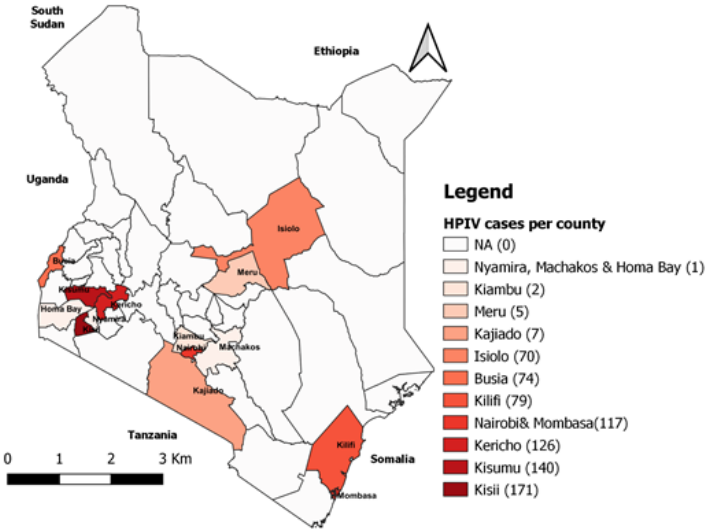
*Human respiratory syncytial virus (HRSV), human parainfluenza virus (HPIV), and human adenoviruses (HAdVs)

The cases of HRSV, HPIV and HAdV distribution varied geographically by county (Fig 14). Kisii county had the highest number of HRSV cases (n=121), while Meru county had the lowest. Besides, Kisii county had the highest number of HPIV cases (N=171), while Nyamira, Machakos, and Homa Bay counties had the lowest number (n=1). Nairobi county had a high number of HAdV cases (n=114), while Kiambu county had a low number (n=1).

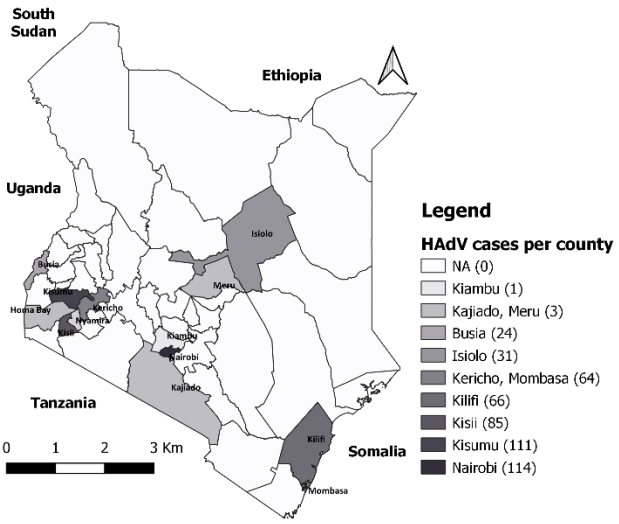
Figure 14. Geographical distribution of (a) Human respiratory syncytial virus (HRSV); (b) Human parainfluenza virus (HPIV); and (c) Human adenoviruses (HAdV) cases per county in Kenya (2007-2013).



a)



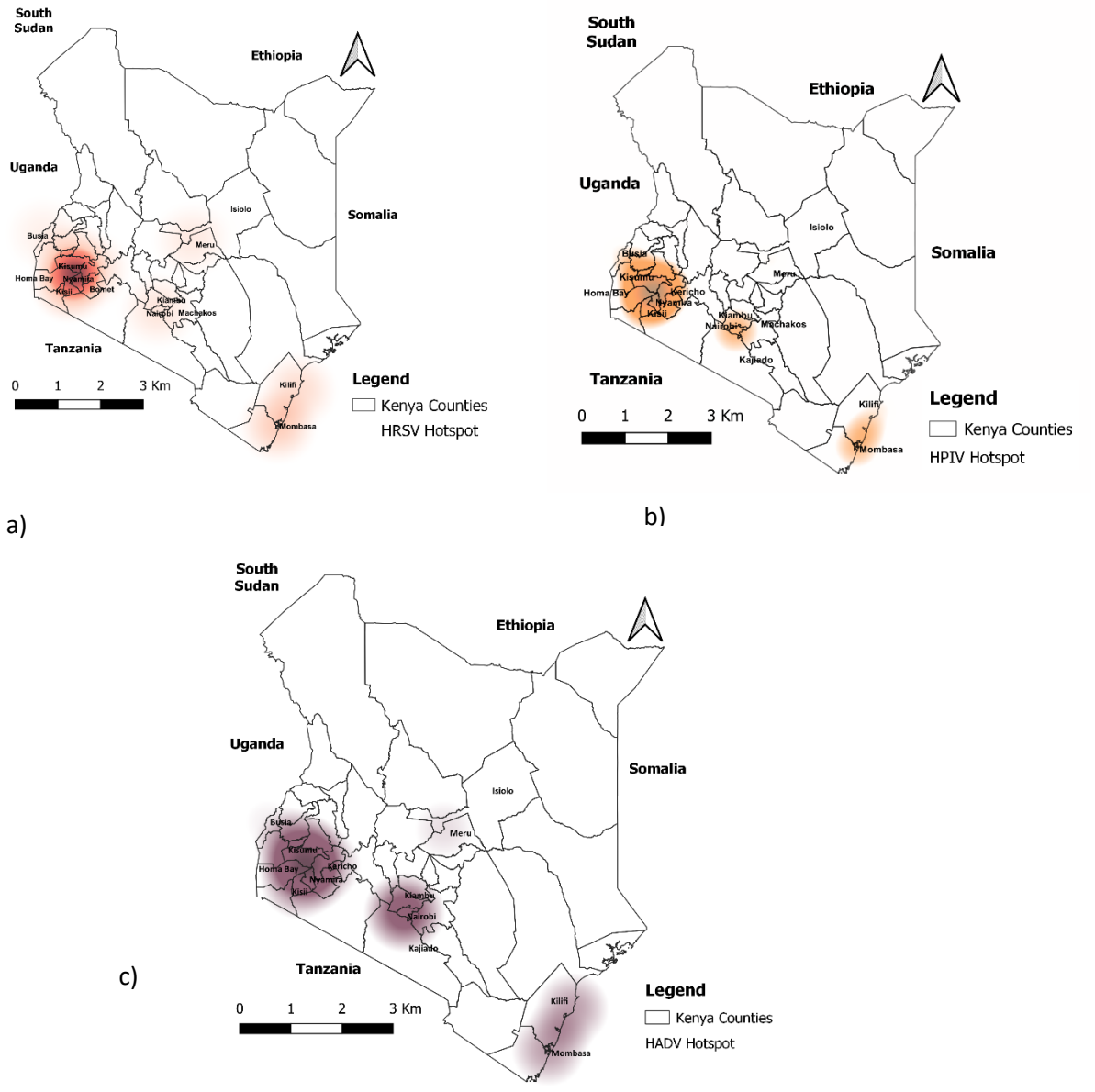
b)



c)

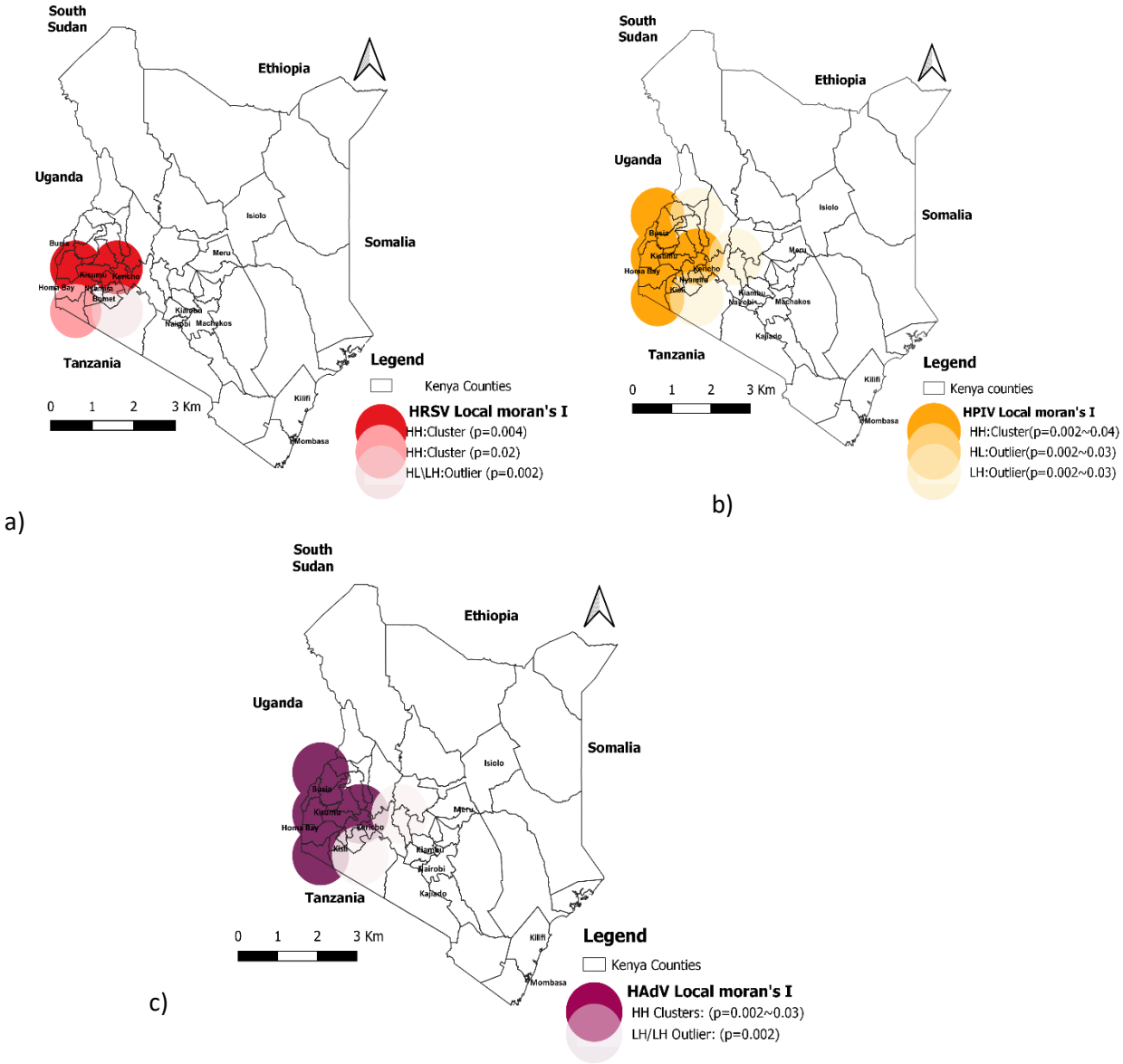
Kernel density estimate revealed the regions with a high density of cases for HRSV, HPIV, and HAdVs hotspots (Fig 15). The locations were denoted by the color of red, orange and purple respectively. HRSV hotspots were identified in the western and coastal regions. HPIV hotspots were found in the coastal, central, and western regions. Similarly, HAdV hotspots were observed in the coastal, central, and western regions.

Figure 15. The geographical location of (a) Human respiratory syncytial virus (HRSV); (b) Human parainfluenza virus (HPIV); and (c) Human adenoviruses (HAdV) hotspots in Kenya (2007-2013)



The Local Moran's I indicated spatial autocorrelation with significant local hotspots or clusters of HRSV, HPIV, and HAdVs (Fig 16). The three respiratory viruses had a significant positive autocorrelation of local clusters in the western region of the country.

Figure 16. Geographical locations significantly associated with (a) Human respiratory syncytial virus (HRSV); (b) Human parainfluenza virus (HPIV); and (c) Human adenoviruses (HAdV) hotspots/clusters in Kenya (2007-2013)



HRSV had a positive hotspot or cluster (high-high/HH) with a p-value (p=0.004) that covered counties including Kericho, Kisumu, and other adjacent counties. In addition, a positive HRSV hotspot (high-high/HH) was noted with a statistically significant p-value (p=0.02) in the adjacent area of HomaBay county. However, the observed HRSV cases in the adjacent area of the Bomet county were an outlier cluster (High-Low/HL or Low-High/LH) with a p-value (p=0.002).

HPIV positive hotspots (high-high/HH) were found in Busia, Kisumu, HomaBay, and neighbouring counties, with p-values ranging from (p=0.002) to (p=0.04). The adjacent region contained outlier clusters (High-Low/HL or Low-High/LH) of HPIV cases with p-values ranging from (p=0.002) to (p=0.03).

HAdV positive hotspots (high-high/HH) were identified in Busia, Kisumu, HomaBay, and neighbouring counties, with p-values ranging from (p=0.002) to (p=0.03). Outlier clusters (High-Low/HL or Low-High/LH) with p=0.03 were found in neighbouring areas.

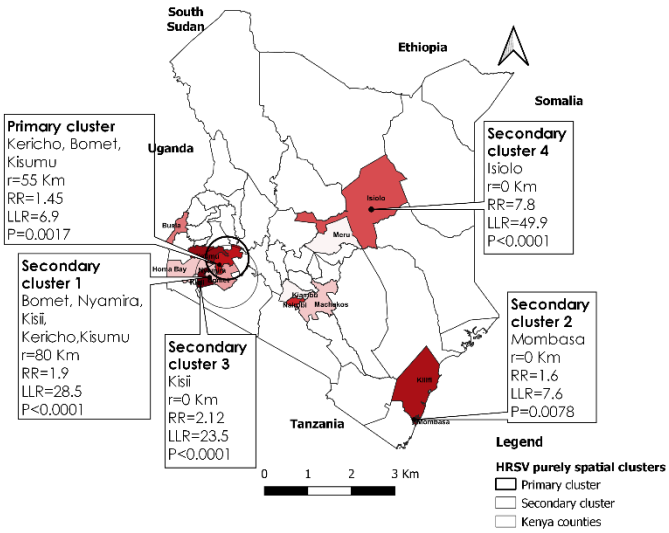
The results of the purely spatial scan statistic revealed statistically significant primary and secondary spatial clusters (P <0.05) for HRSV, HPIV, and HAdVs occurrence (Fig 17).

The HRSV cases had a primary cluster with a 55Km radius in the western region, the cluster covered Kericho, Bomet, and Kisumu counties. There was also an overlapping secondary cluster with an 80-kilometer radius that included Nyamira and Kisii counties. Other secondary clusters were less likely and had a radius of below a kilometer.

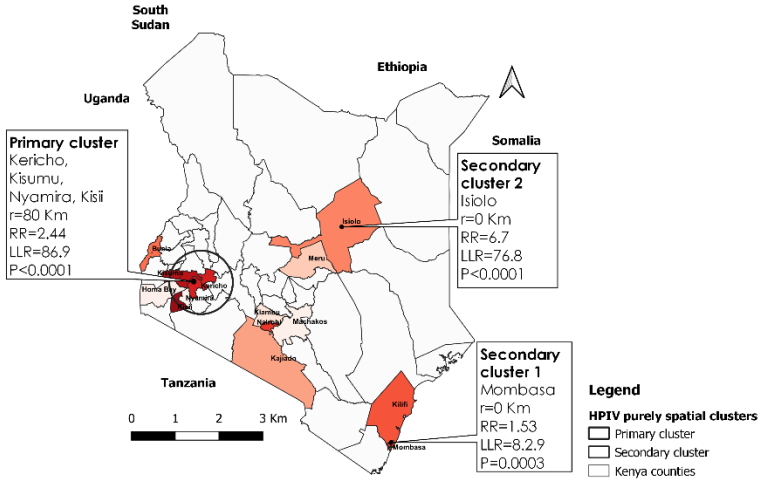
A primary cluster of HPIV was identified over the western region with 80Km radius, this cluster covered Kericho, Kisumu, Nyamira, and Kisii counties. The secondary clusters were found in different regions including the coastal area (Mombasa County) and eastern north region (Isiolo County) with a radius of less than a Km.

HAdVs primary cluster was located within 80Km radius covering Kericho, Kisumu, and Kisii counties. A secondary cluster of HAdVs with less than a 1 Km radius was identified in Isiolo County.

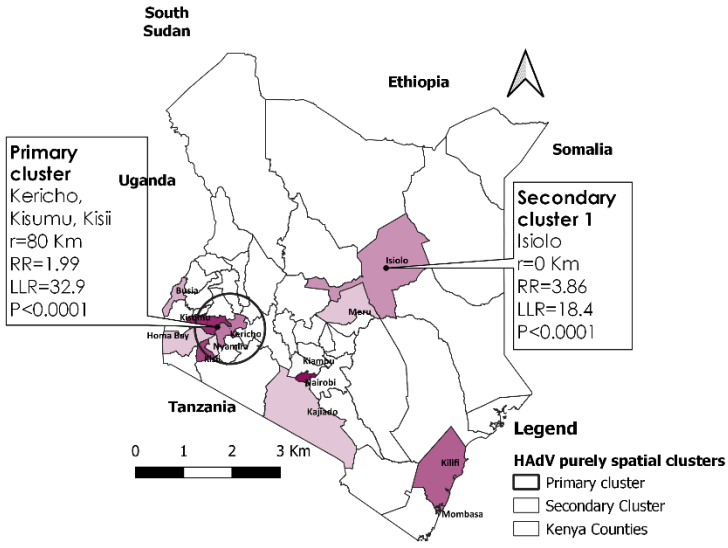
Figure 17. Purely spatial clustering of (a) Human respiratory syncytial virus (HRSV); (b) Human parainfluenza virus (HPIV); and (c) Human adenoviruses (HAdV) cases in Kenya (2007-2013)



a)



b)

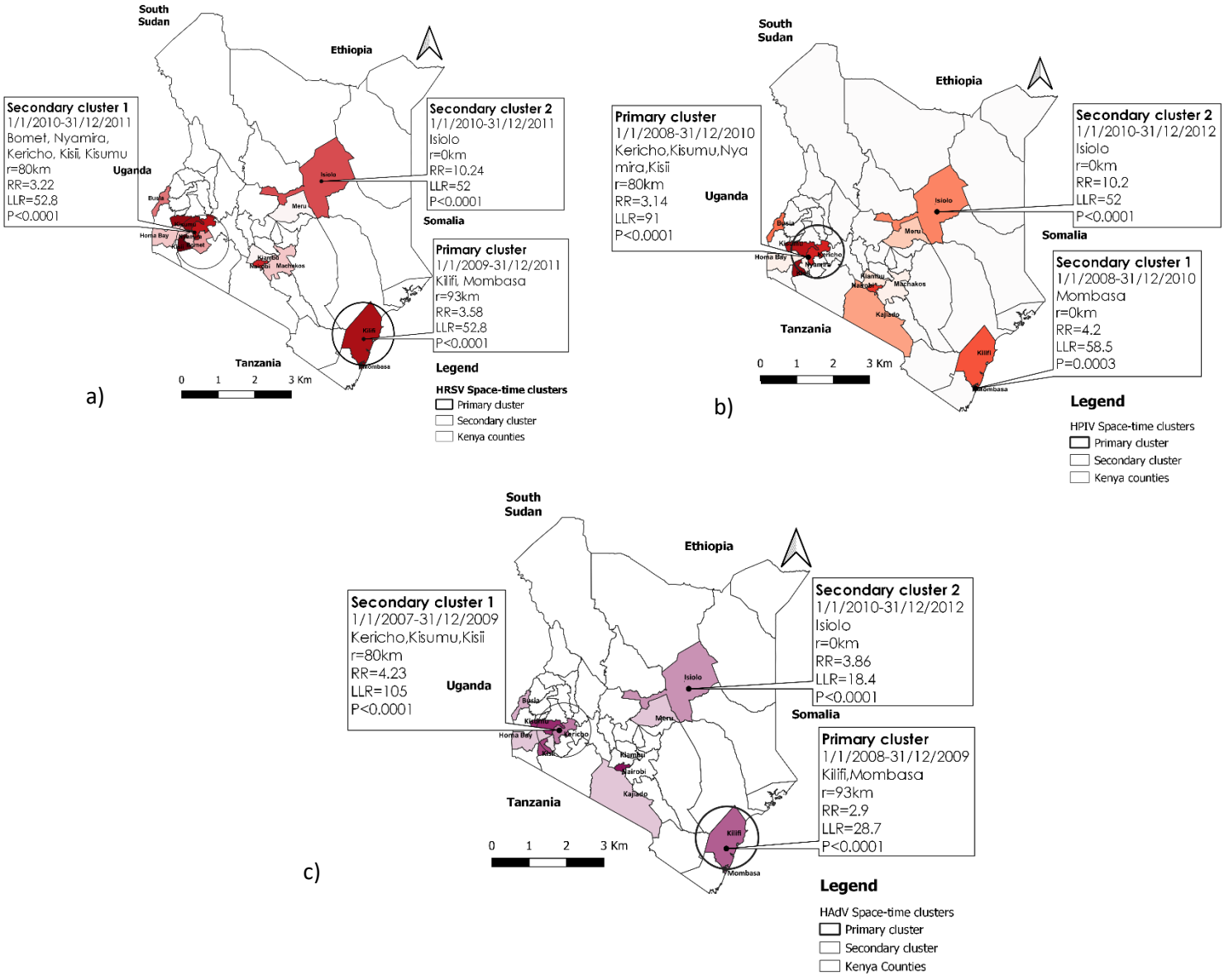


c)

*r: Radius; RR: Relative risk; LLR:Log likelihood Ratio; P: Probability Value

The spatial and temporal distribution of HRSV, HPIV and HAdV cases in Kenya was revealed by spatiotemporal cluster analysis, indicating distinct characteristics (Fig 18).

Figure 18. Spatiotemporal clustering of (a) Human respiratory syncytial virus (HRSV); (b) Human parainfluenza virus (HPIV); and (c) Human adenoviruses (HAdV) cases in Kenya (2007-2013)



*r: Radius; RR: Relative risk; LLR:Log likelihood Ratio; P: Probability Value

HRSV's primary cluster was identified with a 93Km radius in the coastal region. The cluster covered Mombasa and Kilifi counties from 2009 to 2011. A secondary cluster of HRSV was found in the western region with an 80 Km radius covering Bomet, Nyamira, Kisii, Kericho, and Kisumu Counties and occurred from 2010 to 2011. The HPIV primary cluster occurred in the western region from 2008 to 2010, with a radius of 80 kilometers that covered Kericho, Kisumu, Nyamira, and Kisii counties. Both secondary clusters identified in Mombasa and Isiolo counties had a radius of less than one Km and the clusters occurred at different time periods of 2008-2012 and 2010-2012 respectively.

The primary cluster of HAdVs occurred in the coastal region, including Kilifi and Mombasa counties with a 93-kilometer radius, the cases were documented from 2008 to 2009. From 2007 to 2009, a secondary cluster of HAdVs occurred in the western region, covering Kericho, Kisumu, and Kisii counties within an 80-kilometer radius. Besides, another HAdVs secondary cluster was recorded in Isiolo county from 2010 to 2012 with a radius of less than a Km.

CHAPTER V: DISCUSSION AND CONCLUSIONS

5. 1. Discussion

In response to the World Health Organization's International Health Regulations of 2005 (WHO IHR 2005), the majority of EAC partner states established ILI and/or SARI surveillance systems in collaboration with WHO to strengthen global health security. The first influenza and other respiratory surveillance program were established in Kenya (2006), followed by Uganda (2007), Rwanda (2008), and Tanzania (2009)[377,378]. South Sudan and Burundi had no known surveillance programs [379]. Only data from Kenya, Tanzania, and Uganda were available during the systematic review and meta-analysis (2007-2020).

The overall HRSV pooled prevalence was estimated at 11% in EAC, which is nearly similar to a previous estimated figure of 14.6% pooled prevalence in Africa among people with ARTIs [380]. From other geographical regions, HRSV pooled prevalence was estimated at 18.7% among patients with ART in China [381]; this estimate was higher than that reported in EAC. However, HRSV pooled prevalence was 22% among SARI patients in China, reported in the same review [381]. This estimate was consistent with the findings of the review among the SARI population in EAC. Although the Chinese study found a higher pooled prevalence of HRSV (26.5%) among infants, the data in this study revealed that the HRSV pooled prevalence of 10% was the same for those under five and those aged five years and above in EAC. These estimate could be attributed to the studies' population size, sampling methods, distribution, study period, and studies' design among others.

In EAC, the overall HPIV pooled prevalence was 9%. Previously, some studies reported HPIV prevalence estimates that were closer to this. Thus, in Cameroon, 7.5% of people with ILI had HPIV in 2012 [382], which was slightly higher than the HPIV pooled prevalence of 5% found in this systematic review for ILI patients. In Latin America, the estimated HPIV prevalence of 3.2% was slightly lower among people with ILI [383]. This systematic review, on the other hand, discovered a 16% HPIV prevalence among SARI patients, which was higher than 4.8% reported among SARI patients in China [384]. The HPIV pooled prevalence of 14% among patients aged five years and older confirms previous findings from other studies conducted in the same age

groups [100,114,115,385]. The estimates were higher than that of 6% found in younger patients aged below five years.

The overall HAdV pooled prevalence was 13% in EAC. This figure is slightly higher than the 9.8% reported in an individual study conducted in the Eastern Mediterranean region [386]. The difference could be attributed to the distinct geographical location, population and disease syndromes in the documented studies. In 2017, a study conducted in Senegal by Niang *et al.* reported 30.8% of HAdV prevalence in participants with ILI [387]. In contrast, the3% HAdV pooled prevalence among ILI participants recorded in the review was much lower. The source of differences may result in population demographics or other external determinants of the studies. On the other hand, a pooled prevalence of 30% HAdV was identified in individuals of five years and above. From other studies, among college students in the United States, a lower figure of 15% HAdV was reported by Biggs *et al*. in 2018 [388].

Furthermore, 15% HAdV prevalence was found in under five years old through the systematic review in EAC, whereas a study conducted among children with SARI in India found 8.8% HAdV prevalence [389]. The differences in prevalence perceived among studies could be attributable to the heterogeneity in the studies' population by disease severity, age groups, and geographical location. Besides, these variations in prevalence may be due to the population sample size, the sampling methodology, or the diverse diagnostic techniques used among studies.

There were several limitations encountered during the systematic review carried in EAC for the period of 2007 to 2020. The systematic searches were limited to the most accessible and widely used medical literature databases, such as Medline and Global Index Medicus. However, unpublished literature from major public health institutions and research programs in the EAC was used to supplement the search. Furthermore, there were significant sources of heterogeneity in the studies collated to estimate HRSV, HPIV, and HAdV pooled prevalence by disease syndromes, age group, and location. Heterogeneity may also have been influenced by other variables, including the length of the study period, study design, and laboratory technique which were documented. For example, while the majority of studies used highly sensitive and specific diagnostic such as PCR to detect these viruses, studies that used less sensitive diagnostic methods

were likely to have underestimated prevalence. Also, the source of heterogeneity may have been subjected to undocumented variables such as participants' selection which may also have differed among the studies. This might likely lead to a higher prevalence among studies in which severe illness (SARI) patients were enrolled, as opposed to ILI patients.

Furthermore, the small sample size of eligible studies limited the power to detect differences, including in subgroup analysis. For example, not all EAC countries were represented, and Tanzania and Uganda each had only one study. The small sample size may result from various factors including government policy and priorities, lack of documentation, limited funding, inaccessible databases, the complex regulations of information sharing, and difficulties with the publication of data. Also, the extreme values of prevalence have introduced a computational complexity that restricted the reporting of the confidence intervals of the I^2 values.

Additionally, during the systematic review, only studies with defined medical conditions such as ILI and SARI or ARTIs, in general, were included. Studies with asymptomatic participants were excluded. The results of this systematic review cannot be extrapolated to the general population. For example, the symptomatic populations included in the review likely had a higher prevalence of these viruses than the asymptomatic population. It was considered necessary to exclude asymptomatic cases to avoid overdiagnosis, and bias from including patients who were carriers of these respiratory viruses.

The systematic review's strengths included documenting the EAC's concurrent HRSV, HPIV, and HAdV pooled prevalence. In addition, the meta-analysis reported HRSV, HPIV, and HAdV prevalence estimates using a pre-defined protocol, two independent investigators, and robust search strategies. All eligible studies were evaluated for well-defined study characteristics, study heterogeneity, and bias. There was no significant publication bias detected between studies, and the majority of the eligible studies had a low risk of in-study bias. The sensitivity analysis results were comparable to the crude estimates, indicating the robustness of the systematic review and meta-analysis.

In Kenya, influenza and other respiratory viruses' surveillance program was conducted at eight hospitals representing the country geographical regions. The morbidity burden of ILI caused by HRSV, HPIV, and HAdVs was found to be substantial at all hospital sites, with these viruses

contributing 3.1%, 5.3% and 3.3% of ILI respectively. These figures, however, were lower than those previously reported in the systematic review [123]. These differences may have resulted from the fact that systematic review and meta-analysis have the power to synthesize the evidence from several studies. Other factors including the study population may have the influence, since morbidity burden was described from the ILI population only.

HRSV, HPIV, and HAdVs infections were more likely found in infants than other age groups, with the prevalence of 4%, 6%, and 4% respectively. These findings were not surprising given that infants are not known to be immune to these infections. These respiratory viruses are easily transmitted within households and can cause multiple episodes of infection [390]. It is expected that under five years age group seek medical care than those above five years age group. It is also expected these respiratory viruses cause severe illness in under five than above five years age group. However, the prevalence of these respiratory viruses varies per population, location, time and other influencing factors. Multiple HPIV subtype infections suggested a possible co-circulation. Co-morbidity with other respiratory viruses and co-infections among HPIV subtypes, on the other hand, were beyond the scope of this investigation.

The proportion of HRSV, HPIV and HAdV infections was higher at sites in the coastal tropical savanna (Malindi and Port-Reitz) and western tropical forest climatic regions (Kisii, and Kericho). Furthermore, climatic factors have been shown to be an important driver of viral respiratory infection dynamics [391]. HRSV cases increased from January to June, with a seasonal peak around April-May, coinciding with Kenya's rainy season. In addition, moderate rainfall (150-200mm) had a positive impact on HRSV occurrence. This finding was consistent with previous studies conducted in the tropics that described similar trends and indicated an association between RSV respiratory infections and rainfall [392–394].

HRSV exhibited clear seasonality during the surveillance period (2007-2013), occurring more frequently from January through June. Climate parameters including warm air temperature (19-22.9°C), and hot land surface temperature (≥40°C) were suitable for HRSV circulation. This was consistent with other reports which found a positive association between increasing HRSV incidence and the higher monthly average temperature in the tropics [394–396]. The temperature has been a well-described metrological predictor of HRSV infections. In contrast, neither HPIV nor HAdVs showed a clear seasonality. There was also no correlation between temperature or

rainfall and either HPIV or HAdV. These findings support previously documented evidence that reported clear seasonal patterns for HRSV but not HPIV or HAdV [197].

There were unanswered questions when defining the morbidity burden of ILI caused by HRSV, HPIV, or HAdV. This was primarily due to the scope, which could not be explored for several reasons. For example, whereas the morbidity burden of ILI caused by the influenza virus as a major viral aetiology was not explored here, it has been previously reported from the same surveillance system [397].

Other respiratory viruses, on the other hand, were not investigated as potential causes of the ILI morbidity burden. Furthermore, possible co-infections of HRSV, HPIV or HAdV with other viruses were not investigated. In the absence of ILI denominators at surveillance sites, the ILI morbidity burden of the three respiratory viruses may not be generalized. Particularly, the estimates may not be able to be extrapolated to the underlying population at risk. The large population of study participants (91%) aged below 5 years suggests limited generalizability as well as less power in investigating associations in other age groups. Unmeasured environmental or temporal confounding factors, on the other hand, may also have influenced the associations observed.

Despite these weaknesses, there were significant strengths that increased the power of the investigation. This included large sample size, an extensive study period, and a broad geographic region covering the entire country. Besides, the study used reliable sources of data from a robust surveillance network, the use of a pre-defined protocol, and stratified analysis.

From 2007 to 2013, the spatial and temporal patterns of HRSV, HPIV, and HAdV occurrence demonstrated characteristics of influenza-like illness (ILI) distribution in Kenya. The three respiratory viruses were found in each ILI surveillance site. Surveillance sites were located throughout Kenya, including the Western-Nyanza, Rift Valley, Central, Eastern, and Coastal regions. HRSV was found in 13 counties, with Kisii County having the highest number of cases. The Western region was identified as the major hotspot by Kernel density estimation (KDE) and confirmed by local spatial autocorrelation. HRSV primary cluster in the Western region was purely spatial by the scan of statistics. However, the spatial-temporal scan of statistics revealed that HRSV cases clustered in the Coastal region between 2009 and 2011. This was not surprising because

there was also an HRSV hotspot observed in the coastal region by KDE. Besides, HRSV has been identified among the most common pathogens causing acute respiratory tract infections in outpatients in Kenya's coastal region [117]. In addition, the space-time pattern of HRSV showed primary and secondary clusters for both Western and Coastal regions respectively. The HRSV clusters could be attributed to regional population characteristics, social and climate factors. Previous research has associated HRSV infections with several factors, including climatic factors [391,398]. The most common climatic conditions associated with HRSV cases were rainfall and warm temperatures, which characterize the climate of the Western and Coastal regions [399].

HPIV was found in 14 counties, with Kisii County having the highest number of cases. KDE indicated a major HPIV hotspot in the Western region. Other HPIV hotspots, however, have been identified in the coastal and central regions. The Western HPIV hotspot was statistically significant, according to the local spatial autocorrelation. This was confirmed via the purely spatial scan statistics. HPIV had been previously described in the Western region among the etiologies of fever, and respiratory infections [400,401]. The space-time analysis revealed the occurrence of the HPIV cluster in the Western region from 2008 to 2010. In Kenya, unlike with HRSV infections, HPIV infections had an erratic distribution with no clear seasonality [399]. Furthermore, no significant climate parameters were associated with HPIV infections, as observed in other studies published elsewhere [197]. HPIV clusters could thus be attributed to factors other than climatic parameters.

HAdV had been identified in 11 counties, with Nairobi County having the highest number of cases. A major HAdV hotspot was observed in the Western region, in addition to hotspots found in the coastal and central regions. There was a significant spatial autocorrelation of HAdV major hotspot with the Western region. This observation was in agreement with the HAdV primary cluster identified in the same region by the purely spatial scan statistics. Several studies have described the occurrence of HAdV in the Western region [400–403]. However, space-time analysis revealed that the HAdV primary cluster occurred from 2008 to 2009 in the Coastal region. The HAdV cluster in the Western region, on the other hand, was secondary and occurred from 2007 to 2009. In Kenya, there were no seasonality patterns or climate parameters associated with HAdV infection distribution. Only warm temperatures were suggested to have a positive effect on infections [399]. However, other factors such as population demographics, health, and social-economic

determinants have been described in the literature [183,404,405]. The seasonality trends assessment revealed the purely temporal distribution of HRSV, HPIV and HAdV from 2007 to 2013 has been described previously (Publication in press). Although the data derived from the population census allowed to perform spatial-temporal analysis, the results should be interpreted with caution. For example, the use of annual population projection may not accurately reflect the actual population per county [325]. Similarly, retrospective data may not be reflective of the current experience. Although data limitations may affect the results of spatial-temporal analysis, the approach utilized for the analysis suggests potentially important public health interventions. Scan statistics are a known approach to effectively detect disease clusters in the spatial and temporal model [406–409]. It is commonly used for retrospective and perspective routine data collected from disease surveillance programs. These outputs may provide insights to identify clusters for rapidly planning and executing interventions.

5.2. Conclusions and Recommendations

In conclusion, the findings of this investigation indicate that human adenoviruses, human respiratory syncytial virus and parainfluenza virus are prevalent in Kenya, Tanzania, and Uganda. These three respiratory viruses contribute substantially to ARTIs in the EAC partner states with available data, particularly among those with severe disease and those aged five and above. In Kenya, HRSV, HPIV, and HAdVs also contributed to ILI morbidity burden. Infants were significantly affected. HRSV had a clear seasonal pattern and was associated with climate parameters, contrary to HPIV and HAdVs in Kenya. The findings of this study also suggested that hotspots (clusters) for RSV, HPIV, and HAdV occurred in the Western and Coastal regions of Kenya from 2007 to 2013. The Western region appeared more prone to the occurrence of the three respiratory viruses irrespective of the time. Continued surveillance for HRSV, HPIV and HAdVs is recommended to monitor and better describe changes in morbidity caused by these non-influenza respiratory viruses to the population in Kenya. Also, an event-based surveillance system should be established in the western and Coast regions to capture the occurrence of HRSV, HPIV, and HAdVs outbreaks. Further surveillance should include the population of all age categories, but with a particular focus on the elderly because there is a gap in the knowledge of respiratory diseases in this population in Kenya and the EAC.

CHAPTER VI: REFERENCES

1. Legand A, Briand S, Shindo N, Brooks WA, de Jong MD, Farrar J, et al. Addressing the public health burden of respiratory viruses: the Battle against Respiratory Viruses (BRaVe) Initiative. Future Virology. 2013 Sep 16;8(10):953–68.

2. Noor R, Maniha SM. A brief outline of respiratory viral disease outbreaks: 1889–till date on the public health perspectives. VirusDis [Internet]. 2020 Sep 2 [cited 2020 Nov 30]; Available from: https://doi.org/10.1007/s13337-020-00628-5

3. Johnson NPAS, Mueller J. Updating the accounts: global mortality of the 1918-1920 "Spanish" influenza pandemic. Bull Hist Med. 2002;76(1):105–15.

4. Max Roser, Hannah Ritchie, Esteban Ortiz-Ospina, Joe Hasell. Coronavirus Pandemic (COVID-19) [Internet]. Our World in Data. 2020 [cited 2021 Jul 2]. Available from: https://ourworldindata.org/covid-cases

5. Peltola V, Ruuskanen O. Respiratory Viral Infections in Developing Countries: Common, Severe, and Unrecognized. Clin Infect Dis. 2008 Jan 1;46(1):58–60.

6. Kenmoe S, Bigna JJ, Fatawou Modiyingi A, Ndangang MS, Ngoupo PA, Simo FBN, et al. Case fatality rate and viral aetiologies of acute respiratory tract infections in HIV positive and negative people in Africa: The VARIAFRICA-HIV systematic review and meta-analysis. J Clin Virol. 2019;117:96–102.

7. Pneumonia Etiology Research for Child Health (PERCH) Study Group. Causes of severe pneumonia requiring hospital admission in children without HIV infection from Africa and Asia: the PERCH multi-country case-control study. Lancet. 2019 31;394(10200):757–79.

8. Morris JA, Blount RE, Savage RE. Recovery of Cytopathogenic Agent from Chimpanzees with Goryza. Proceedings of the Society for Experimental Biology and Medicine. 1956 Jul 1;92(3):544–9.

9. Chanock R, Roizman B, Myers R. RECOVERY FROM INFANTS WITH RESPIRATORY ILLNESS OF A VIRUS RELATED TO CHIMPANZEE CORYZA AGENT (CCA)ISOLATION, PROPERTIES AND CHARACTERIZATION. Am J Epidemiol. 1957 Nov 1;66(3):281–90.

10. Walsh EE, Hall CB. 160 - Respiratory Syncytial Virus (RSV). In: Bennett JE, Dolin R, Blaser MJ, editors. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases (Eighth Edition) [Internet]. Philadelphia: W.B. Saunders; 2015 [cited 2020 Dec 1]. p. 1948-1960.e3. Available from: http://www.sciencedirect.com/science/article/pii/B9781455748013001600

11. Afonso CL, Amarasinghe GK, Bányai K, Bào Y, Basler CF, Bavari S, et al. TAXONOMY OF THE ORDER MONONEGAVIRALES: UPDATE 2016. Arch Virol. 2016 Aug;161(8):2351–60.

12. Collins PL, Fearns R, Graham BS. Respiratory Syncytial Virus: Virology, Reverse Genetics, and Pathogenesis of Disease. Curr Top Microbiol Immunol. 2013;372:3–38.

13. Hall CB. Respiratory Syncytial Virus and Parainfluenza Virus. New England Journal of Medicine. 2001 Jun 21;344(25):1917–28.

14. Sullender WM. Respiratory Syncytial Virus Genetic and Antigenic Diversity. Clin Microbiol Rev. 2000 Jan;13(1):1–15.

15. Henrickson KJ. Parainfluenza Viruses. Clin Microbiol Rev. 2003 Apr;16(2):242–64.

16. Vainionpää R, Hyypiä T. Biology of parainfluenza viruses. Clin Microbiol Rev. 1994 Apr;7(2):265–75.

17. Phan MVT, Arron G, GeurtsvanKessel CH, Huisman RC, Molenkamp R, Koopmans MPG, et al. Complete Genome Characterization of Eight Human Parainfluenza Viruses from the Netherlands. Microbiol Resour Announc [Internet]. 2019 Apr 11 [cited 2021 Apr 8];8(15). Available from: https://mra.asm.org/content/8/15/e00125-19

18. Burrell CJ, Howard CR, Murphy FA. Chapter 18 - Adenoviruses. In: Burrell CJ, Howard CR, Murphy FA, editors. Fenner and White's Medical Virology (Fifth Edition) [Internet]. London: Academic Press; 2017 [cited 2020 Dec 1]. p. 263–71. Available from: http://www.sciencedirect.com/science/article/pii/B9780123751560000187

19. Ginsberg HS. The life and times of adenoviruses. Adv Virus Res. 1999;54:1–13.

20. Crenshaw BJ, Jones LB, Bell CR, Kumar S, Matthews QL. Perspective on Adenoviruses: Epidemiology, Pathogenicity, and Gene Therapy. Biomedicines [Internet]. 2019 Aug 19 [cited 2020 Dec 1];7(3). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6784011/

21. Jones MS, Harrach B, Ganac RD, Gozum MMA, dela Cruz WP, Riedel B, et al. New Adenovirus Species Found in a Patient Presenting with Gastroenteritis. J Virol. 2007 Jun;81(11):5978–84.

22. Aoki K, Ishiko H, Konno T, Shimada Y, Hayashi A, Kaneko H, et al. Epidemic Keratoconjunctivitis Due to the Novel Hexon-Chimeric-Intermediate 22,37/H8 Human Adenovirus. J Clin Microbiol. 2008 Oct;46(10):3259–69.

23. Ghebremedhin B. Human adenovirus: Viral pathogen with increasing importance. Eur J Microbiol Immunol (Bp). 2014 Mar;4(1):26–33.

24. Kennedy MA, Parks RJ. Adenovirus Virion Stability and the Viral Genome: Size Matters. Mol Ther. 2009 Oct;17(10):1664–6.

25. Gaunt ER, Harvala H, McIntyre C, Templeton KE, Simmonds P. Disease burden of the most commonly detected respiratory viruses in hospitalized patients calculated using the disability adjusted life year (DALY) model. J Clin Virol. 2011 Nov;52(3):215–21.

26. Shi T, McAllister DA, O'Brien KL, Simoes EAF, Madhi SA, Gessner BD, et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in young children in 2015: a systematic review and modelling study. Lancet. 2017 Sep 2;390(10098):946–58.

27. Shi T, Arnott A, Semogas I, Falsey AR, Openshaw P, Wedzicha JA, et al. The etiological role of common respiratory viruses in acute respiratory infections in older adults: a systematic review and meta-analysis. S569 [Internet]. 2020 Nov 1 [cited 2020 Dec 3]; Available from: http://spiral.imperial.ac.uk/handle/10044/1/67864

28. Fendrick AM, Monto AS, Nightengale B, Sarnes M. The economic burden of non-influenza-related viral respiratory tract infection in the United States. Arch Intern Med. 2003 Feb 24;163(4):487–94.

29. Díez-Domingo J, Pérez-Yarza EG, Melero JA, Sánchez-Luna M, Aguilar MD, Blasco AJ, et al. Social, economic, and health impact of the respiratory syncytial virus: a systematic search. BMC Infect Dis. 2014 Oct 30;14:544.

30. Bont L, Checchia PA, Fauroux B, Figueras-Aloy J, Manzoni P, Paes B, et al. Defining the Epidemiology and Burden of Severe Respiratory Syncytial Virus Infection Among Infants and Children in Western Countries. Infect Dis Ther. 2016 Sep;5(3):271–98.

31. Tam CC, Yeo KT, Tee N, Lin R, Mak TM, Thoon KC, et al. Burden and Cost of Hospitalization for Respiratory Syncytial Virus in Young Children, Singapore - Volume 26, Number 7—July 2020 - Emerging Infectious Diseases journal - CDC. [cited 2020 Dec 3]; Available from: https://wwwnc.cdc.gov/eid/article/26/7/19-0539_article

32. GBD 2016 Lower Respiratory Infections Collaborators. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of lower respiratory infections in 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Infect Dis. 2018 Nov;18(11):1191–210.

33. Fleming DM, Taylor RJ, Lustig RL, Schuck-Paim C, Haguinet F, Webb DJ, et al. Modelling estimates of the burden of Respiratory Syncytial virus infection in adults and the elderly in the United Kingdom. BMC Infect Dis. 2015 Oct 23;15:443.

34. Ranmuthugala G, Brown L, Lidbury BA. Respiratory syncytial virus--the unrecognised cause of health and economic burden among young children in Australia. Commun Dis Intell Q Rep. 2011 Jun;35(2):177–84.

35. Zhou JA, Schweinle JE, Lichenstein R, Walker RE, King JC. Severe Illnesses Associated With Outbreaks of Respiratory Syncytial Virus and Influenza in Adults. Clin Infect Dis. 2020 Feb 14;70(5):773–9.

36. Geis S, Prifert C, Weissbrich B, Lehners N, Egerer G, Eisenbach C, et al. Molecular Characterization of a Respiratory Syncytial Virus Outbreak in a Hematology Unit in Heidelberg, Germany. Journal of Clinical Microbiology. 2013 Jan 1;51(1):155–62.

37. Ryu S, Kim BI, Chun BC. An outbreak of respiratory tract infection due to Respiratory Syncytial Virus-B in a postpartum center. J Infect Chemother. 2018 Sep;24(9):689–94.

38. Mlinaric-Galinovic G, Vilibic-Cavlek T, Ljubin-Sternak S, Drazenovic V, Galinovic I, Tomic V, et al. Eleven consecutive years of respiratory syncytial virus outbreaks in Croatia. Pediatrics International. 2009;51(2):237–40.

39. Chiu SS, Chan K-H, Chen H, Young BW, Lim W, Wong WH-S, et al. Virologically Confirmed Population-based Burden of Hospitalization Caused by Respiratory Syncytial Virus, Adenovirus, and Parainfluenza Viruses in Children in Hong Kong. The Pediatric Infectious Disease Journal. 2010 Dec;29(12):1088–92.

40. Tang JW, Lam TT, Zaraket H, Lipkin WI, Drews SJ, Hatchette TF, et al. Global epidemiology of non-influenza RNA respiratory viruses: data gaps and a growing need for surveillance. Lancet Infect Dis. 2017 Oct;17(10):e320–6.

41. Wang X, Nair H. Global burden of acute lower respiratory infection associated with human parainfluenza virus in children under five years for 2018: a systematic review and meta-analysis [Internet]. University of Edinburgh, Usher Institute, Center for Global Health; 2020 [cited 2020 Dec 3]. Available from: https://datashare.is.ed.ac.uk/handle/10283/3700

42. Wang X. Global burden of acute lower respiratory infection (ALRI) associated with influenza virus, human metapneumovirus, and human parainfluenza virus among children under five years [Internet] [Ph.D.]. University of Edinburgh; 2020 [cited 2020 Dec 27]. Available from: https://doi.org/10.7488/era/405

43. Rafeek RAM, Divarathna MVM, Noordeen F. A review on disease burden and epidemiology of childhood parainfluenza virus infections in Asian countries. Reviews in Medical Virology. n/a(n/a):e2164.

44. Gregianini TS, Seadi CF, Neto LDZ, Martins LG, Muller GC, Straliotto SM, et al. A 28-year study of human parainfluenza in Rio Grande do Sul, Southern Brazil. Journal of Medical Virology. 2019;91(8):1423–31.

45. Ruampunpong H, Payungporn S, Samransamruajkit R, Pratheepamornkul T, Theamboonlers A, Poovorawan Y. Human parainfluenza virus infection in Thai children with lower respiratory tract infection from 2010 to 2013. Southeast Asian J Trop Med Public Health. 2014 May;45(3):610–21.

46. DeGroote NP, Haynes AK, Taylor C, Killerby ME, Dahl RM, Mustaquim D, et al. Human parainfluenza virus circulation, United States, 2011-2019. J Clin Virol. 2020;124:104261.

47. Abedi GR, Prill MM, Langley GE, Wikswo ME, Weinberg GA, Curns AT, et al. Estimates of Parainfluenza Virus-Associated Hospitalizations and Cost Among Children Aged Less Than 5 Years in the United States, 1998–2010. J Pediatric Infect Dis Soc. 2016 Mar;5(1):7–13.

48. Maziarz RT, Sridharan P, Slater S, Meyers G, Post M, Erdman DD, et al. Control of an Outbreak of Human Parainfluenza Virus 3 in Hematopoietic Stem Cell Transplant Recipients. Biology of Blood and Marrow Transplantation. 2010 Feb 1;16(2):192–8.

49. Abiko C, Mizuta K, Aoki Y, Ikeda T, Itagaki T, Noda M, et al. An Outbreak of Parainfluenza Virus Type 4 Infections among Children with Acute Respiratory Infections during the 2011–2012 Winter Season in Yamagata, Japan. Japanese Journal of Infectious Diseases. 2013;66(1):76–8.

50. Harvala H, Gaunt E, McIntyre C, Roddie H, Labonte S, Curran E, et al. Epidemiology and clinical characteristics of parainfluenza virus 3 outbreak in a Haemato-oncology unit. Journal of Infection. 2012 Sep 1;65(3):246–54.

51. Li H-J, Du J, Yang Y-N, Cui Y, Xi L, Wang S, et al. Outbreak of Human Parainfluenza Virus Type 1 in a Kindergarten from China, 2018. J Pediatr Infect Dis. 2020 Jan;15(1):25–30.

52. Civljak R, Kosutic-Gulija T, Slovic A, Huljev E, Turcic N, Mestrovic T, et al. An Outbreak of Human Parainfluenza Virus 3 (Phylogenetic Subcluster C5) Infection among Adults at a Residential Care Facility for the Disabled in Croatia, 2018. INT. 2019;62(5–6):174–81.

53. Lafolie J, Mirand A, Salmona M, Lautrette A, Archimbaud C, Brebion A, et al. Severe Pneumonia Associated with Adenovirus Type 55 Infection, France, 2014. Emerg Infect Dis. 2016 Nov;22(11):2012–4.

54. Sun B, He H, Wang Z, Qu J, Li X, Ban C, et al. Emergent severe acute respiratory distress syndrome caused by adenovirus type 55 in immunocompetent adults in 2013: a prospective observational study. Crit Care. 2014 Aug 12;18(4):456.

55. Cheng J, Qi X, Chen D, Xu X, Wang G, Dai Y, et al. Epidemiology and transmission characteristics of human adenovirus type 7 caused acute respiratory disease outbreak in military trainees in East China. Am J Transl Res. 2016 May 15;8(5):2331–42.

56. Jin Y, Zhang R, Xie Z, Yan K, Gao H, Song J, et al. Prevalence of adenovirus in children with acute respiratory tract infection in Lanzhou, China. Virol J [Internet]. 2013 Aug 29 [cited 2020 Dec 5];10. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4015357/

57. Zhao S, Wan C, Ke C, Seto J, Dehghan S, Zou L, et al. Re-emergent Human Adenovirus Genome Type 7d Caused an Acute Respiratory Disease Outbreak in Southern China After a Twenty-one Year Absence. Sci Rep [Internet]. 2014 Dec 8 [cited 2020 Dec 5];4. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4258649/

58. Tang L, Wang L, Tan X, Xu W. Adenovirus serotype 7 associated with a severe lower respiratory tract disease outbreak in infants in Shaanxi Province, China. Virol J [Internet]. 2011 Jan 18 [cited 2020 Dec 5];8. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3030507/

59. Kajon AE, Dickson LM, Metzgar D, Houng H-S, Lee V, Tan B-H. Outbreak of Febrile Respiratory Illness Associated with Adenovirus 11a Infection in a Singapore Military Training Camp. J Clin Microbiol. 2010 Apr;48(4):1438–41.

60. Yusof MA, Rashid TRTA, Thayan R, Othman KA, Abu Hasan N, Adnan N, et al. Human Adenovirus Type 7 Outbreak in Police Training Center, Malaysia, 2011. Emerg Infect Dis. 2012 May;18(5):852–4.

61. Kujawski SA, Lu X, Schneider E, Blythe D, Boktor S, Farrehi J, et al. Outbreaks of Adenovirus-associated Respiratory Illness on 5 College Campuses in the United States, 2018–2019. Clin Infect Dis [Internet]. [cited 2020 Dec 5]; Available from: https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa465/5823941

62. Hakim FA, Tleyjeh IM. Severe adenovirus pneumonia in immunocompetent adults: a case report and review of the literature. Eur J Clin Microbiol Infect Dis. 2008;27(2):153–8.

63. Duan YL, Zhu Y, Xu BP, Li CC, Chen AH, Deng L, et al. [Multicenter study of human adenovirus infection in pediatric community-acquired pneumonia in China]. Zhonghua Er Ke Za Zhi. 2019 Jan 2;57(1):27–32.

64. Li L, Woo YY, de Bruyne JA, Nathan AM, Kee SY, Chan YF, et al. Epidemiology, clinical presentation and respiratory sequelae of adenovirus pneumonia in children in Kuala Lumpur, Malaysia. PLoS One. 2018;13(10):e0205795.

65. Ho A. Viral pneumonia in adults and older children in sub-Saharan Africa - epidemiology, aetiology, diagnosis and management. Pneumonia (Nathan). 2014;5(Suppl 1):18–29.

66. Jennings LC. Symposium on viral respiratory disease surveillance. Influenza Other Respir Viruses. 2010 May;4(Suppl 2):1.

67. Ziegler T, Mamahit A, Cox NJ. 65 years of influenza surveillance by a World Health Organization-coordinated global network. Influenza and Other Respiratory Viruses. 2018;12(5):558–65.

68. Feldman C, Shaddock E. Epidemiology of lower respiratory tract infections in adults. Expert Review of Respiratory Medicine. 2019 Jan 2;13(1):63–77.

69. Brouard J, Vabret A, Nimal-Cuvillon D, Bach N, Bessière A, Arion A, et al. [Epidemiology of acute upper and lower respiratory tract infections in children]. Rev Prat. 2007 Oct 31;57(16):1759–66.

70. Grief SN. Upper Respiratory Infections. Prim Care. 2013 Sep;40(3):757–70.

71. Pavia AT. Viral Infections of the Lower Respiratory Tract: Old Viruses, New Viruses, and the Role of Diagnosis. Clin Infect Dis. 2011 May 1;52(suppl_4):S284–9.

72. Carroll KC, Adams LL. Lower Respiratory Tract Infections. Microbiology Spectrum [Internet]. 2016 Jul 15 [cited 2020 Dec 8];4(4). Available from: https://www.asmscience.org/content/journal/microbiolspec/10.1128/microbiolspec.DMIH2-0029-2016

73. Aston SJ, Rylance J. Community-Acquired Pneumonia in Sub-Saharan Africa. Semin Respir Crit Care Med. 2016 Dec;37(6):855–67.

74. Aliberti S, Chalmers JD, Pletz MW. Community-Acquired Pneumonia: European Respiratory Monograph. European Respiratory Society; 2014. 306 p.

75. Duenas Meza E, Jaramillo CA, Correa E, Torres-Duque CA, García C, González M, et al. Virus and Mycoplasma pneumoniae prevalence in a selected pediatric population with acute asthma exacerbation. J Asthma. 2016;53(3):253–60.

76. Radin JM, Katz MA, Tempia S, Talla Nzussouo N, Davis R, Duque J, et al. Influenza surveillance in 15 countries in Africa, 2006-2010. J Infect Dis. 2012 Dec 15;206 Suppl 1:S14-21.

77. Niang MN, Diop NS, Fall A, Kiori DE, Sarr FD, Sy S, et al. Respiratory viruses in patients with influenza-like illness in Senegal: Focus on human respiratory adenoviruses. PLoS One [Internet]. 2017 Mar 22 [cited 2020 Dec 9];12(3). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5362214/

78. Shi T, McLean K, Campbell H, Nair H. Aetiological role of common respiratory viruses in acute lower respiratory infections in children under five years: A systematic review and meta–analysis. J Glob Health [Internet]. [cited 2020 Dec 9];5(1). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4593292/

79. Marangu D, Zar HJ. Childhood pneumonia in low-and-middle-income countries: An update. Paediatric Respiratory Reviews. 2019 Nov 1;32:3–9.

80. O'Callaghan-Gordo C, Díez-Padrisa N, Abacassamo F, Pérez-Breña P, Casas I, Alonso PL, et al. Viral acute respiratory infections among infants visited in a rural hospital of southern Mozambique. Trop Med Int Health. 2011 Sep;16(9):1054–60.

81. Kabego L, Balol'Ebwami S, Kasengi JB, Miyanga S, Bahati YL, Kambale R, et al. Human respiratory syncytial virus: prevalence, viral co-infections and risk factors for lower respiratory tract infections in children under 5 years of age at a general hospital in the Democratic Republic of Congo. J Med Microbiol. 2018 Apr;67(4):514–22.

82. Kwofie TB, Anane YA, Nkrumah B, Annan A, Nguah SB, Owusu M. Respiratory viruses in children hospitalized for acute lower respiratory tract infection in Ghana. Virol J. 2012 Apr 10;9:78.

83. Ahmed JA, Katz MA, Auko E, Njenga MK, Weinberg M, Kapella BK, et al. Epidemiology of respiratory viral infections in two long-term refugee camps in Kenya, 2007-2010. BMC Infect Dis. 2012 Jan 17;12:7.

84. Enan KA, Nabeshima T, Kubo T, Buerano CC, El Hussein ARM, Elkhidir IM, et al. Survey of causative agents for acute respiratory infections among patients in Khartoum-State, Sudan, 2010-2011. Virol J. 2013 Oct 25;10:312.

85. Bobossi Serengbe G, Gody J-C, Fioboy R, Nakoune E. Étiologie virale des infections respiratoires aiguës de l'enfant à Bangui. Arch Pediatr. 2015 Mar;22(3):324–5.

86. Breiman RF, Cosmas L, Njenga M, Williamson J, Mott JA, Katz MA, et al. Severe acute respiratory infection in children in a densely populated urban slum in Kenya, 2007-2011. BMC Infect Dis. 2015 Feb 25;15:95.

87. Mohamed GA, Ahmed JA, Marano N, Mohamed A, Moturi E, Burton W, et al. Etiology and Incidence of Viral Acute Respiratory Infections Among Refugees Aged 5 Years and Older in Hagadera Camp, Dadaab, Kenya. Am J Trop Med Hyg. 2015 Dec;93(6):1371–6.

88. Kenmoe S, Tchendjou P, Vernet M, Moyo-Tetang S, Mossus T, Njankouo-Ripa M, et al. Viral etiology of severe acute respiratory infections in hospitalized children in Cameroon, 2011–2013. Influenza Other Respir Viruses. 2016 Sep;10(5):386–93.

89. Sanicas M, Forleo E, Pozzi G, Diop D. A review of the surveillance systems of influenza in selected countries in the tropical region. Pan Afr Med J. 2014;19:121.

90. EAC Secretariat. East African Community Facts and Figures - 2019 [Internet]. 2019. Available from: https://www.eac.int/overview-of-eac

91. MacPherson DW, Gushulak BD, Macdonald L. Health and foreign policy: influences of migration and population mobility. Bull World Health Organ. 2007 Mar;85(3):200–6.

92. Hammitt LL, Kazungu S, Morpeth SC, Gibson DG, Mvera B, Brent AJ, et al. A Preliminary Study of Pneumonia Etiology Among Hospitalized Children in Kenya. Clin Infect Dis. 2012 Apr 1;54(suppl_2):S190–9.

93. O'Meara WP, Mott JA, Laktabai J, Wamburu K, Fields B, Armstrong J, et al. Etiology of pediatric fever in western Kenya: a case-control study of falciparum malaria, respiratory viruses, and streptococcal pharyngitis. Am J Trop Med Hyg. 2015 May;92(5):1030–7.

94. Berkley JA, Munywoki P, Ngama M, Kazungu S, Abwao J, Bett A, et al. Viral etiology of severe pneumonia among Kenyan infants and children. JAMA. 2010 May 26;303(20):2051–7.

95. Lutwama JJ, Bakamutumaho B, Kayiwa JT, Chiiza R, Namagambo B, Katz MA, et al. Clinic- and hospital-based sentinel influenza surveillance, Uganda 2007-2010. J Infect Dis. 2012 Dec 15;206 Suppl 1:S87-93.

96. Katz MA, Muthoka P, Emukule GO, Kalani R, Njuguna H, Waiboci LW, et al. Results From the First Six Years of National Sentinel Surveillance for Influenza in Kenya, July 2007–June 2013. PLOS ONE. 2014 Jun 23;9(6):e98615.

97. Jeremy Sueker J, Blazes DL, Johns MC, Blair PJ, Sjoberg PA, Tjaden JA, et al. Influenza and respiratory disease surveillance: the US military's global laboratory-based network. Influenza Other Respir Viruses. 2010 May;4(3):155–61.

98. Symekhier SMI, Ochieng WO, Simwa J. Prevalence of viral aetiologies in children with acute respiratory infections in Nairobi, Kenya. Tanzania Journal of Health Research [Internet]. 2009 [cited 2021 Apr 16];11(2). Available from: https://www.ajol.info/index.php/thrb/article/view/45210

99. Rachel A. Achilla, Wallace D. Bulimo, Janet M. Majanja, Meshack O. Wadegu, Silvanus O. Mukunzi, Josphat Mwangi, et al. Respiratory Adenovirus Species Circulating In Kenya from 2007-2010. African Journal of Pharmacology and Therapeutics [Internet]. 2012 Dec 31 [cited 2017 Dec 25];1(4). Available from: http://journals.uonbi.ac.ke/ajpt/article/view/1110

100. Stephen Balinandi, Barnabas Bakamutumaho, John T. Kayiwa, Juliette Ongus, Joseph Oundo, Anna C. Awor, et al. The viral aetiology of influenzalike illnesses in Kampala and Entebbe, Uganda, 2008. Afr J Lab Med [Internet]. 2013 Jun 24 [cited 2018 Sep 28];2(1). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5637772/

101. Mmbaga Vida, Maria Kelly, Matonya Miriam, Mwalongo Vumilia, Mosha Fausta, Moshi Solomoni, et al. The Prevalence of Influenza and other Respiratory Viruses among ILI and SARI patients in Tanzania, from January 2016 to August 2017. In Carlton Hotel Antananarivo, Madagascar; 2018. Available from: http://www.anise-network.org/

102. Tin Tin Htar M, Yerramalla MS, Moïsi JC, Swerdlow DL. The burden of respiratory syncytial virus in adults: a systematic review and meta-analysis. Epidemiol Infect. 2020 Feb 13;148:e48.

103. Bardach A, Rey-Ares L, Cafferata ML, Cormick G, Romano M, Ruvinsky S, et al. Systematic review and meta-analysis of respiratory syncytial virus infection epidemiology in Latin America. Reviews in Medical Virology. 2014;24(2):76–89.

104. Zhang Y, Yuan L, Zhang Y, Zhang X, Zheng M, Kyaw MH. Burden of respiratory syncytial virus infections in China: Systematic review and meta–analysis. J Glob Health [Internet]. [cited 2020 Dec 24];5(2). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4676581/

105. Salimi V, Tavakoli-Yaraki M, Yavarian J, Bont L, Mokhtari-Azad T. Prevalence of human respiratory syncytial virus circulating in Iran. J Infect Public Health. 2016 Apr;9(2):125–35.

106. Pangesti KNA, El Ghany MA, Kesson AM, Hill-Cawthorne GA. Respiratory syncytial virus in the Western Pacific Region: a systematic review and meta-analysis. J Glob Health. 2019 Dec;9(2):020431.

107. Yassine HM, Sohail MU, Younes N, Nasrallah GK. Systematic Review of the Respiratory Syncytial Virus (RSV) Prevalence, Genotype Distribution, and Seasonality in Children from the Middle East and North Africa (MENA) Region. Microorganisms. 2020 May 11;8(5).

108. Kenmoe S, Bigna JJ, Well EA, Simo FBN, Penlap VB, Vabret A, et al. Prevalence of human respiratory syncytial virus infection in people with acute respiratory tract infections in Africa: A systematic review and meta-analysis. Influenza Other Respir Viruses. 2018 Nov;12(6):793–803.

109. Ho A. Viral pneumonia in adults and older children in sub-Saharan Africa — epidemiology, aetiology, diagnosis and management. Pneumonia. 2014 Dec;5(1):18–29.

110. Brandenburg AH, van Beek R, Moll HA, Osterhaus ADME, Claas ECJ. G Protein Variation in Respiratory Syncytial Virus Group A Does Not Correlate with Clinical Severity. J Clin Microbiol. 2000 Oct;38(10):3849–52.

111. Hirsh S, Hindiyeh M, Kolet L, Regev L, Sherbany H, Yaary K, et al. Epidemiological Changes of Respiratory Syncytial Virus (RSV) Infections in Israel. PLOS ONE. 2014 Mar 3;9(3):e90515.

112. S. M. I. Symekhier, W. O. Ochieng, J. Simwa. Prevalence of viral aetiologies in children with acute respiratory infections in Nairobi, Kenya. Tanzania Journal of Health Research [Internet]. 2009 Jan 1 [cited 2018 Sep 28];11(2). Available from: https://www.ajol.info/index.php/thrb/article/view/45210

113. Gideon O. Emukule, Sammy Khagayi, Meredith L. McMorrow, Rachel Ochola, Nancy Otieno, Marc-Alain Widdowson, et al. The burden of influenza and RSV among inpatients and outpatients in rural western Kenya, 2009-2012. PLoS ONE. 2014;9(8):e105543.

114. Joyce Uchi Nyiro, Patrick Munywoki, Everlyn Kamau, Charles Agoti, Alex Gichuki, Timothy Etyang, et al. Surveillance of respiratory viruses in the outpatient setting in rural coastal Kenya: baseline epidemiological observations. Wellcome Open Res. 2018;3:89.

115. Gedi A. Mohamed, Jamal A. Ahmed, Nina Marano, Abdinoor Mohamed, Edna Moturi, Wagacha Burton, et al. Etiology and Incidence of Viral Acute Respiratory Infections Among Refugees Aged 5 Years and Older in Hagadera Camp, Dadaab, Kenya. Am J Trop Med Hyg. 2015 Dec;93(6):1371–6.

116. Jamal A. Ahmed, Mark A. Katz, Eric Auko, M. Kariuki Njenga, Michelle Weinberg, Bryan K. Kapella, et al. Epidemiology of respiratory viral infections in two long-term refugee camps in Kenya, 2007-2010. BMC Infect Dis. 2012 Jan 17;12:7.

117. Nyiro JU, Munywoki P, Kamau E, Agoti C, Gichuki A, Etyang T, et al. Surveillance of respiratory viruses in the outpatient setting in rural coastal Kenya: baseline epidemiological observations. Wellcome Open Res [Internet]. 2018 Jul 25 [cited 2020 Dec 26];3. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6081997/

118. Lim FJ, Blyth CC, Fathima P, de Klerk N, Moore HC. Record linkage study of the pathogen-specific burden of respiratory viruses in children. Influenza Other Respir Viruses. 2017 Nov;11(6):502–10.

119. Chittaganpitch M, Waicharoen S, Yingyong T, Praphasiri P, Sangkitporn S, Olsen SJ, et al. Viral etiologies of influenza-like illness and severe acute respiratory infections in Thailand. Influenza Other Respir Viruses. 2018 Jul;12(4):482–9.

120. Rafeek RAM, Divarathna MVM, Noordeen F. A review on disease burden and epidemiology of childhood parainfluenza virus infections in Asian countries. Reviews in Medical Virology. n/a(n/a):e2164.

121. Villaran MV, García J, Gomez J, Arango AE, Gonzales M, Chicaiza W, et al. Human parainfluenza virus in patients with influenza-like illness from Central and South America during 2006–2010. Influenza Other Respir Viruses. 2014 Mar;8(2):217–27.

122. Steffens A, Finelli L, Whitaker B, Fowlkes A. Population-based Surveillance for Medically Attended Human Parainfluenza Viruses From the Influenza Incidence Surveillance Project, 2010-2014. Pediatr Infect Dis J. 2016;35(7):717–22.

123. Umuhoza T, Bulimo WD, Oyugi J, Musabyimana JP, Kinengyere AA, Mancuso JD. Prevalence of human respiratory syncytial virus, parainfluenza and adenoviruses in East Africa Community partner states of Kenya, Tanzania, and Uganda: A systematic review and meta-analysis (2007-2020). PLoS One. 2021;16(4):e0249992.

124. Zhao H, Harris RJ, Ellis J, Donati M, Pebody RG. Epidemiology of parainfluenza infection in England and Wales, 1998–2013: any evidence of change? Epidemiology & Infection. 2017 Apr;145(6):1210–20.

125. Bose ME, Shrivastava S, He J, Nelson MI, Bera J, Fedorova N, et al. Sequencing and analysis of globally obtained human parainfluenza viruses 1 and 3 genomes. PLoS One. 2019;14(7):e0220057.

126. Guo L, Gonzalez R, Zhou H, Wu C, Vernet G, Wang Z, et al. Detection of three human adenovirus species in adults with acute respiratory infection in China. Eur J Clin Microbiol Infect Dis. 2012 Jun 1;31(6):1051–8.

127. Nakamura H, Fujisawa T, Suga S, Taniguchi K, Nagao M, Ito M, et al. Species differences in circulation and inflammatory responses in children with common respiratory adenovirus infections. J Med Virol. 2018 May;90(5):873–80.

128. Echavarria M, Maldonado D, Elbert G, Videla C, Rappaport R, Carballal G. Use of PCR To Demonstrate Presence of Adenovirus Species B, C, or F as Well as Coinfection with Two Adenovirus Species in Children with Flu-Like Symptoms. Journal of Clinical Microbiology. 2006 Feb 1;44(2):625–7.

129. Scott MK, Chommanard C, Lu X, Appelgate D, Grenz L, Schneider E, et al. Human Adenovirus Associated with Severe Respiratory Infection, Oregon, USA, 2013–2014. Emerg Infect Dis. 2016 Jun;22(6):1044–51.

130. Akello JO, Kamgang R, Barbani MT, Suter-Riniker F, Leib SL, Ramette A. Epidemiology of Human Adenoviruses: A 20-Year Retrospective Observational Study in Hospitalized Patients in Bern, Switzerland. Clin Epidemiol. 2020 Apr 5;12:353–66.

131. Wu X, Lu X, Schneider E, Ahmed JA, Njenga MK, Breiman RF, et al. Reassessment of high prevalence human adenovirus detections among residents of two refugee centers in Kenya under surveillance for acute respiratory infections. J Med Virol. 2019 Mar;91(3):385–91.

132. Metzgar D, Osuna M, Yingst S, Rakha M, Earhart K, Elyan D, et al. PCR analysis of egyptian respiratory adenovirus isolates, including identification of species, serotypes, and coinfections. J Clin Microbiol. 2005 Nov;43(11):5743–52.

133. Wang Y-F, Shen F-C, Wang S-L, Kuo P-H, Tsai H-P, Liu C-C, et al. Molecular Epidemiology and Clinical Manifestations of Adenovirus Respiratory Infections in Taiwanese Children. Medicine (Baltimore). 2016 May;95(18):e3577.

134. Wang S-L, Chi C-Y, Kuo P-H, Tsai H-P, Wang S-M, Liu C-C, et al. High-incidence of human adenoviral co-infections in taiwan. PLoS One. 2013;8(9):e75208.

135. Zheng X, Xu Y, Guan W, Lin L. Regional, age and respiratory-secretion-specific prevalence of respiratory viruses associated with asthma exacerbation: a literature review. Arch Virol. 2018;163(4):845–53.

136. Haque E, Banik U, Monwar T, Anthony L, Adhikary AK. Worldwide increased prevalence of human adenovirus type 3 (HAdV-3) respiratory infections is well correlated with heterogeneous hypervariable regions (HVRs) of hexon. PLOS ONE. 2018 Mar 28;13(3):e0194516.

137. Jafarinejad H, Moghoofei M, Mostafaei S, Salimian J, Azimzadeh Jamalkandi S, Ahmadi A. Worldwide prevalence of viral infection in AECOPD patients: A meta-analysis. Microbial Pathogenesis. 2017 Dec 1;113:190–6.

138. Chen Y, Liu F, Wang C, Zhao M, Deng L, Zhong J, et al. Molecular Identification and Epidemiological Features of Human Adenoviruses Associated with Acute Respiratory Infections in Hospitalized Children in Southern China, 2012-2013. PLOS ONE. 2016 May 12;11(5):e0155412.

139. García J, Sovero M, Laguna-Torres VA, Gomez J, Chicaiza W, Barrantes M, et al. Molecular characterization of adenovirus circulating in Central and South America during the 2006–2008 period. Influenza and Other Respiratory Viruses. 2009;3(6):327–30.

140. Ampuero JS, Ocaña V, Gómez J, Gamero ME, Garcia J, Halsey ES, et al. Adenovirus Respiratory Tract Infections in Peru. PLoS One [Internet]. 2012 Oct 8 [cited 2021 Jan 11];7(10). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3466214/

141. Demian PN, Horton KC, Kajon A, Siam R, Hasanin AMN, Elgohary Sheta A, et al. Molecular identification of adenoviruses associated with respiratory infection in Egypt from 2003 to 2010. BMC Infect Dis. 2014 Jan 30;14(1):50.

142. Lekana-Douki SE, Nkoghe D, Drosten C, Ngoungou EB, Drexler JF, Leroy EM. Viral etiology and seasonality of influenza-like illness in Gabon, March 2010 to June 2011. BMC Infect Dis. 2014 Jul 7;14:373.

143. Niang MN, Diop NS, Fall A, Kiori DE, Sarr FD, Sy S, et al. Respiratory viruses in patients with influenza-like illness in Senegal: Focus on human respiratory adenoviruses. PLoS One [Internet]. 2017 Mar 22 [cited 2021 Jan 11];12(3). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5362214/

144. Kutter JS, Spronken MI, Fraaij PL, Fouchier RA, Herfst S. Transmission routes of respiratory viruses among humans. Current Opinion in Virology. 2018 Feb 1;28:142–51.

145. Gralton J, Tovey E, McLaws M-L, Rawlinson WD. The role of particle size in aerosolised pathogen transmission: A review. J Infect. 2011 Jan;62(1):1–13.

146. Piedimonte G, Perez MK. ALTERNATIVE MECHANISMS FOR RESPIRATORY SYNCYTIAL VIRUS (RSV) INFECTION AND PERSISTENCE: Could RSV Be Transmitted Through the Placenta and Persist into Developing Fetal Lungs? Curr Opin Pharmacol. 2014 Jun;0:82–8.

147. Piedimonte G, Walton C, Samsell L. Vertical Transmission of Respiratory Syncytial Virus Modulates Pre- and Postnatal Innervation and Reactivity of Rat Airways. PLoS One [Internet]. 2013 Apr 18 [cited 2021 Jan 1];8(4). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3630224/

148. Burke CW, Bridges O, Brown S, Rahija R, Russell CJ. Mode of Parainfluenza Virus Transmission Determines the Dynamics of Primary Infection and Protection from Reinfection. PLOS Pathogens. 2013 Nov 21;9(11):e1003786.

149. Stobnicka A, Gołofit-Szymczak M, Wójcik-Fatla A, Zając V, Korczyńska-Smolec J, Górny RL. Prevalence of Human Parainfluenza Viruses and Noroviruses Genomes on Office Fomites. Food Environ Virol. 2018 Jun;10(2):133–40.

150. Russell KL, Broderick MP, Franklin SE, Blyn LB, Freed NE, Moradi E, et al. Transmission Dynamics and Prospective Environmental Sampling of Adenovirus in a Military Recruit Setting. J Infect Dis. 2006 Oct 1;194(7):877–85.

151. La Rosa G, Fratini M, Della Libera S, Iaconelli M, Muscillo M. Viral infections acquired indoors through airborne, droplet or contact transmission. Ann Ist Super Sanita. 2013;49(2):124–32.

152. Walker CM, Ko G. Effect of ultraviolet germicidal irradiation on viral aerosols. Environ Sci Technol. 2007 Aug 1;41(15):5460–5.

153. Lessler J, Reich NG, Brookmeyer R, Perl TM, Nelson KE, Cummings DAT. Incubation periods of acute respiratory viral infections: a systematic review. Lancet Infect Dis. 2009 May;9(5):291–300.

154. Basnayake TL, Morgan LC, Chang AB. The global burden of respiratory infections in indigenous children and adults: A review. Respirology. 2017 Nov;22(8):1518–28.

155. Sommer C, Resch B, Simões EAF. Risk factors for severe respiratory syncytial virus lower respiratory tract infection. Open Microbiol J. 2011;5:144–54.

156. Chan PWK, Chew FT, Tan TN, Chua KB, Hooi PS. Seasonal variation in respiratory syncytial virus chest infection in the tropics. Pediatric Pulmonology. 2002;34(1):47–51.

157. Pica N, Bouvier NM. Environmental factors affecting the transmission of respiratory viruses. Curr Opin Virol. 2012 Feb;2(1):90–5.

158. Pang J, Jin J, Loh JP, Tan BH, Koh WHV, Ng SH, et al. Risk factors for febrile respiratory illness and mono-viral infections in a semi-closed military environment: a case-control study. BMC Infect Dis [Internet]. 2015 Jul 25 [cited 2021 Jan 1];15. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4514976/

159. Matias G, Taylor R, Haguinet F, Schuck-Paim C, Lustig R, Shinde V. Estimates of hospitalization attributable to influenza and RSV in the US during 1997–2009, by age and

risk status. BMC Public Health [Internet]. 2017 Mar 21 [cited 2021 Jan 1];17. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5359836/

160. Gunville CF, Sontag MK, Stratton KA, Ranade DJ, Abman SH, Mourani PM. Scope and impact of early and late preterm infants admitted to the PICU with respiratory illness. J Pediatr. 2010 Aug;157(2):209-214.e1.

161. Simon A, Ammann RA, Wilkesmann A, Eis-Hübinger AM, Schildgen O, Weimann E, et al. Respiratory syncytial virus infection in 406 hospitalized premature infants: results from a prospective German multicentre database. Eur J Pediatr. 2007 Dec 1;166(12):1273–83.

162. Kristensen K, Stensballe LG, Bjerre J, Roth D, Fisker N, Kongstad T, et al. Risk factors for respiratory syncytial virus hospitalisation in children with heart disease. Arch Dis Child. 2009 Oct;94(10):785–9.

163. Madhi SA, Schoub B, Simmank K, Blackburn N, Klugman KP. Increased burden of respiratory viral associated severe lower respiratory tract infections in children infected with human immunodeficiency virus type-1. The Journal of Pediatrics. 2000 Jul 1;137(1):78–84.

164. Park SY, Kim T, Jang YR, Kim M-C, Chong YP, Lee S-O, et al. Factors predicting life-threatening infections with respiratory syncytial virus in adult patients. Infectious Diseases. 2017 May 4;49(5):333–40.

165. Voraphani N, Stern DA, Wright AL, Guerra S, Morgan WJ, Martinez FD. Risk of current asthma among adult smokers with respiratory syncytial virus illnesses in early life. Am J Respir Crit Care Med. 2014 Aug 15;190(4):392–8.

166. Shi T, Balsells E, Wastnedge E, Singleton R, Rasmussen ZA, Zar HJ, et al. Risk factors for respiratory syncytial virus associated with acute lower respiratory infection in children under five years: Systematic review and meta-analysis. J Glob Health. 2015 Dec;5(2):020416.

167. Paynter S, Ware RS, Lucero MG, Tallo V, Nohynek H, Weinstein P, et al. Malnutrition: a risk factor for severe respiratory syncytial virus infection and hospitalization. Pediatr Infect Dis J. 2014 Mar;33(3):267–71.

168. Choudhuri JA, Ogden LG, Ruttenber AJ, Thomas DSK, Todd JK, Simoes EAF. Effect of altitude on hospitalizations for respiratory syncytial virus infection. Pediatrics. 2006 Feb;117(2):349–56.

169. Munywoki PK, Koech DC, Agoti CN, Lewa C, Cane PA, Medley GF, et al. The Source of Respiratory Syncytial Virus Infection In Infants: A Household Cohort Study In Rural Kenya. J Infect Dis. 2014 Jun 1;209(11):1685–92.

170. Black CP. Systematic review of the biology and medical management of respiratory syncytial virus infection. Respir Care. 2003 Mar;48(3):209–31; discussion 231-233.

171. Resch B. Burden of respiratory syncytial virus infection in young children. World J Clin Pediatr. 2012 Oct 8;1(3):8–12.

172. Shay DK, Holman RC, Newman RD, Liu LL, Stout JW, Anderson LJ. Bronchiolitis-associated hospitalizations among US children, 1980-1996. JAMA. 1999 Oct 20;282(15):1440–6.

173. Shi T, Denouel A, Tietjen AK, Campbell I, Moran E, Li X, et al. Global Disease Burden Estimates of Respiratory Syncytial Virus-Associated Acute Respiratory Infection in Older Adults in 2015: A Systematic Review and Meta-Analysis. J Infect Dis. 2020 Oct 7;222(Supplement_7):S577–83.

174. Nam HH, Ison MG. Respiratory syncytial virus infection in adults. BMJ. 2019 Sep 10;366:l5021.

175. Falsey AR, Hennessey PA, Formica MA, Cox C, Walsh EE. Respiratory Syncytial Virus Infection in Elderly and High-Risk Adults. New England Journal of Medicine. 2005 Apr 28;352(17):1749–59.

176. Pawełczyk M, Kowalski ML. The Role of Human Parainfluenza Virus Infections in the Immunopathology of the Respiratory Tract. Current Allergy and Asthma Reports [Internet]. 2017 [cited 2020 Dec 2];17(3). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7089069/

177. Russell E, Ison MG. Parainfluenza Virus in the Hospitalized Adult. Clin Infect Dis. 2017 Oct 16;65(9):1570–6.

178. Schmidt AC, Schaap-Nutt A, Bartlett EJ, Schomacker H, Boonyaratanakornkit J, Karron RA, et al. Progress in the development of human parainfluenza virus vaccines. Expert Rev Respir Med. 2011 Aug;5(4):515–26.

179. Calvo C, García-García ML, Sanchez-Dehesa R, Román C, Tabares A, Pozo F, et al. Eight Year Prospective Study of Adenoviruses Infections in Hospitalized Children. Comparison with Other Respiratory Viruses. PLOS ONE. 2015 Jul 6;10(7):e0132162.

180. Echavarría M. Adenoviruses in immunocompromised hosts. Clin Microbiol Rev. 2008 Oct;21(4):704–15.

181. Xie L, Zhang B, Zhou J, Huang H, Zeng S, Liu Q, et al. Human adenovirus load in respiratory tract secretions are predictors for disease severity in children with human adenovirus pneumonia. Virology Journal. 2018 Aug 7;15(1):123.

182. Gao W-J, Jin Y, Duan Z-J. [Research progress in human adenovirus]. Bing Du Xue Bao. 2014 Mar;30(2):193–200.

183. Bautista-Gogel J, Madsen CM, Lu X, Sakthivel SK, Froh I, Kamau E, et al. Outbreak of Respiratory Illness Associated With Human Adenovirus Type 7 Among Persons Attending Officer Candidates School, Quantico, Virginia, 2017. The Journal of Infectious Diseases. 2020 Feb 18;221(5):697–700.

184. Lewis PF, Schmidt MA, Lu X, Erdman DD, Campbell M, Thomas A, et al. A Community-Based Outbreak of Severe Respiratory Illness Caused by Human Adenovirus Serotype 14. The Journal of Infectious Diseases. 2009 May 15;199(10):1427–34.

185. Walls T, Shankar AG, Shingadia D. Adenovirus: an increasingly important pathogen in paediatric bone marrow transplant patients. The Lancet Infectious Diseases. 2003 Feb 1;3(2):79–86.

186. Kajon AE, Lamson DM, St. George K. Emergence and re-emergence of respiratory adenoviruses in the United States. Current Opinion in Virology. 2019 Feb 1;34:63–9.

187. Sharma P, Kolawole AO, Core SB, Kajon AE, Excoffon KJDA. Sidestream Smoke Exposure Increases the Susceptibility of Airway Epithelia to Adenoviral Infection. PLOS ONE. 2012 Nov 15;7(11):e49930.

188. Bandaly V, Joubert A, Andres Y, Le Cann P. Adenovirus behavior in air handling unit fiberglass filters. Aerobiologia. 2019 Jun 1;35(2):357–66.

189. Esposito S, Zampiero A, Bianchini S, Mori A, Scala A, Tagliabue C, et al. Epidemiology and Clinical Characteristics of Respiratory Infections Due to Adenovirus in Children Living in Milan, Italy, during 2013 and 2014. PLOS ONE. 2016 Apr 5;11(4):e0152375.

190. Qurei L, Seto D, Salah Z, Azzeh M. A Molecular Epidemiology Survey of Respiratory Adenoviruses Circulating in Children Residing in Southern Palestine. PLOS ONE. 2012 Aug 3;7(8):e42732.

191. Janet S, Broad J, Snape MD. Respiratory syncytial virus seasonality and its implications on prevention strategies. Hum Vaccin Immunother. 2018 02;14(1):234–44.

192. Paynter S. Humidity and respiratory virus transmission in tropical and temperate settings. Epidemiol Infect. 2015 Apr;143(6):1110–8.

193. Ge X, Guo Y, Cheng J, Hu R, Feng X. Epidemiology and Seasonality of Respiratory Viruses Detected from Children with Respiratory Tract Infections in Wuxi, East China. Med Sci Monit. 2018 Mar 30;24:1856–62.

194. Chadha M, Hirve S, Bancej C, Barr I, Baumeister E, Caetano B, et al. Human respiratory syncytial virus and influenza seasonality patterns—Early findings from the WHO global respiratory syncytial virus surveillance. Influenza and Other Respiratory Viruses. 2020;14(6):638–46.

195. Shek LP-C, Lee B-W. Epidemiology and seasonality of respiratory tract virus infections in the tropics. Paediatr Respir Rev. 2003 Jun;4(2):105–11.

196. Lam TT, Tang JW, Lai FY, Zaraket H, Dbaibo G, Bialasiewicz S, et al. Comparative global epidemiology of influenza, respiratory syncytial and parainfluenza viruses, 2010–2015. J Infect. 2019 Oct;79(4):373–82.

197. Li Y, Reeves RM, Wang X, Bassat Q, Brooks WA, Cohen C, et al. Global patterns in monthly activity of influenza virus, respiratory syncytial virus, parainfluenza virus, and metapneumovirus: a systematic analysis. Lancet Glob Health. 2019 Aug;7(8):e1031–45.

198. Price RHM, Graham C, Ramalingam S. Association between viral seasonality and meteorological factors. Sci Rep. 2019 Jan 30;9(1):929.

199. Mullins JA, Lamonte AC, Bresee JS, Anderson LJ. Substantial variability in community respiratory syncytial virus season timing. Pediatr Infect Dis J. 2003 Oct;22(10):857–62.

200. Obando-Pacheco P, Justicia-Grande AJ, Rivero-Calle I, Rodríguez-Tenreiro C, Sly P, Ramilo O, et al. Respiratory Syncytial Virus Seasonality: A Global Overview. The Journal of Infectious Diseases. 2018 Apr 11;217(9):1356–64.

201. Broberg EK, Waris M, Johansen K, Snacken R, Penttinen P, European Influenza Surveillance Network. Seasonality and geographical spread of respiratory syncytial virus epidemics in 15 European countries, 2010 to 2016. Euro Surveill. 2018;23(5).

202. Haynes AK, Manangan AP, Iwane MK, Sturm-Ramirez K, Homaira N, Brooks WA, et al. Respiratory Syncytial Virus Circulation in Seven Countries With Global Disease Detection Regional Centers. The Journal of Infectious Diseases. 2013 Dec 15;208(suppl_3):S246–54.

203. Gamba-Sanchez N, Rodriguez-Martinez CE, Sossa-Briceño MP. Epidemic activity of respiratory syncytial virus is related to temperature and rainfall in equatorial tropical countries. Epidemiology & Infection. 2016 Jul;144(10):2057–63.

204. Moura FEA, Perdigão ACB, Ribeiro JF, Florêncio CMGD, Oliveira FMS, Pereira SAR, et al. Respiratory syncytial virus epidemic periods in an equatorial city of Brazil. Influenza and Other Respiratory Viruses. 2013;7(6):1128–35.

205. Sricharoenchai S. Seasonality of Respiratory Syncytial Virus - Lower Respiratory Tract Infection (RSV-LRTI) in Children in Developing Countries. JHVRV [Internet]. 2016 Jan 11 [cited 2021 Jan 2];3(1). Available from: https://medcraveonline.com/JHVRV/seasonality-of-respiratory-syncytial-virus---lower-respiratory-tract-infection-rsv-lrti-in-children-in-developing-countries.html

206. Hogan AB, Anderssen RS, Davis S, Moore HC, Lim FJ, Fathima P, et al. Time series analysis of RSV and bronchiolitis seasonality in temperate and tropical Western Australia. Epidemics. 2016 Sep;16:49–55.

207. Sundell N, Andersson L-M, Brittain-Long R, Lindh M, Westin J. A four year seasonal survey of the relationship between outdoor climate and epidemiology of viral respiratory tract infections in a temperate climate. J Clin Virol. 2016 Nov;84:59–63.

208. Sundell N, Andersson L-M, Brittain-Long R, Lindh M, Westin J. A four year seasonal survey of the relationship between outdoor climate and epidemiology of viral respiratory tract infections in a temperate climate. J Clin Virol. 2016 Nov;84:59–63.

209. Rose EB, Wheatley A, Langley G, Gerber S, Haynes A. Respiratory Syncytial Virus Seasonality — United States, 2014–2017. MMWR Morb Mortal Wkly Rep. 2018 Jan 19;67(2):71–6.

210. Welliver RCS. Temperature, Humidity, and Ultraviolet B Radiation Predict Community Respiratory Syncytial Virus Activity. The Pediatric Infectious Disease Journal. 2007 Nov;26(11):S29.

211. Lapeña S, Robles MB, Castañón L, Martínez JP, Reguero S, Alonso MP, et al. Climatic factors and lower respiratory tract infection due to respiratory syncytial virus in hospitalised infants in northern Spain. Eur J Epidemiol. 2005;20(3):271–6.

212. Welliver R. The relationship of meteorological conditions to the epidemic activity of respiratory syncytial virus. Paediatric Respiratory Reviews. 2009 Jun 1;10:6–8.

213. Chan PWK, Chew FT, Tan TN, Chua KB, Hooi PS. Seasonal variation in respiratory syncytial virus chest infection in the tropics. Pediatr Pulmonol. 2002 Jul;34(1):47–51.

214. Álvarez-Argüelles ME, Rojo-Alba S, Pérez Martínez Z, Leal Negredo Á, Boga Riveiro JA, Alonso Álvarez MA, et al. New clinical and seasonal evidence of infections by Human Parainfluenzavirus. Eur J Clin Microbiol Infect Dis. 2018 Nov;37(11):2211–7.

215. Liu W-K, Liu Q, Chen D-H, Liang H-X, Chen X-K, Huang W-B, et al. Epidemiology and clinical presentation of the four human parainfluenza virus types. BMC Infect Dis. 2013 Jan 23;13:28.

216. Zhao H, Harris RJ, Ellis J, Donati M, Pebody RG. Epidemiology of parainfluenza infection in England and Wales, 1998-2013: any evidence of change? Epidemiol Infect. 2017 Apr;145(6):1210–20.

217. DeGroote NP, Haynes AK, Taylor C, Killerby ME, Dahl RM, Mustaquim D, et al. Human parainfluenza virus circulation, United States, 2011–2019. J Clin Virol. 2020 Mar;124:104261.

218. Human Parainfluenza Viruses | HPIV Seasons | CDC [Internet]. 2019 [cited 2021 Jan 5]. Available from: https://www.cdc.gov/parainfluenza/seasons.html

219. Fry AM, Curns AT, Harbour K, Hutwagner L, Holman RC, Anderson LJ. Seasonal trends of human parainfluenza viral infections: United States, 1990-2004. Clin Infect Dis. 2006 Oct 15;43(8):1016–22.

220. Maykowski P, Smithgall M, Zachariah P, Oberhardt M, Vargas C, Reed C, et al. Seasonality and clinical impact of human parainfluenza viruses. Influenza Other Respir Viruses. 2018 Nov;12(6):706–16.

221. Gregianini TS, Seadi CF, Zavarize Neto LD, Martins LG, Muller GC, Straliotto SM, et al. A 28-year study of human parainfluenza in Rio Grande do Sul, Southern Brazil. J Med Virol. 2019 Aug;91(8):1423–31.

222. Alonso WJ, Laranjeira BJ, Pereira SAR, Florencio CMGD, Moreno EC, Miller MA, et al. Comparative Dynamics, Morbidity and Mortality Burden of Pediatric Viral Respiratory Infections in an Equatorial City. Pediatr Infect Dis J. 2012 Jan;31(1):e9-14.

223. Dela Cruz CS, Pasnick S, Gross JE, Keller J, Carlos WG, Cao B, et al. Adenovirus Infection and Outbreaks: What You Need to Know. Am J Respir Crit Care Med. 2019 Apr 1;199(7):P13–4.

224. Kolavic-Gray SA, Binn LN, Sanchez JL, Cersovsky SB, Polyak CS, Mitchell-Raymundo F, et al. Large Epidemic of Adenovirus Type 4 Infection among Military Trainees: Epidemiological, Clinical, and Laboratory Studies. Clinical Infectious Diseases. 2002 Oct 1;35(7):808–18.

225. Huh K, Kim I, Jung J, Lee JE, Jhun BW, Gu SH, et al. Prolonged shedding of type 55 human adenovirus in immunocompetent adults with adenoviral respiratory infections. Eur J Clin Microbiol Infect Dis. 2019 Apr;38(4):793–800.

226. Ryan MAK, Gray GC, Smith B, McKeehan JA, Hawksworth AW, Malasig MD. Large Epidemic of Respiratory Illness Due to Adenovirus Types 7 and 3 in Healthy Young Adults. Clinical Infectious Diseases. 2002 Mar 1;34(5):577–82.

227. Singh-Naz N, Brown M, Ganeshananthan M. Nosocomial adenovirus infection: molecular epidemiology of an outbreak. Pediatr Infect Dis J. 1993 Nov;12(11):922–5.

228. Akiyoshi K, Suga T, Fukui K, Taniguchi K, Okabe N, Fujimoto T. Outbreak of epidemic keratoconjunctivitis caused by adenovirus type 54 in a nursery school in Kobe City, Japan in 2008. Jpn J Infect Dis. 2011;64(4):353–5.

229. Hwang S-M, Park D-E, Yang Y-I, Park S-J, Lee H-K, Kim M-J, et al. Outbreak of Febrile Respiratory Illness Caused by Adenovirus at a South Korean Military Training Facility: Clinical and Radiological Characteristics of Adenovirus Pneumonia. Japanese Journal of Infectious Diseases. 2013;66(5):359–65.

230. Yoo H, Gu SH, Jung J, Song DH, Yoon C, Hong DJ, et al. Febrile Respiratory Illness Associated with Human Adenovirus Type 55 in South Korea Military, 2014–2016. Emerg Infect Dis. 2017 Jun;23(6):1016–20.

231. Yu P, Ma C, Nawaz M, Han L, Zhang J, Du Q, et al. Outbreak of acute respiratory disease caused by human adenovirus type 7 in a military training camp in Shaanxi, China. Microbiology and Immunology. 2013;57(8):553–60.

232. Kujawski SA, Lu X, Schneider E, Blythe D, Boktor S, Farrehi J, et al. Outbreaks of adenovirus-associated respiratory illness on five college campuses in the United States. Clin Infect Dis. 2020 Apr 23;

233. Rebelo-de-Andrade H, Pereira C, Gíria M, Prudêncio E, Brito MJ, Calé E, et al. Outbreak of acute respiratory infection among infants in Lisbon, Portugal, caused by human adenovirus serotype 3 and a new 7/3 recombinant strain. J Clin Microbiol. 2010 Apr;48(4):1391–6.

234. James L, Vernon MO, Jones RC, Stewart A, Lu X, Zollar LM, et al. Outbreak of human adenovirus type 3 infection in a pediatric long-term care facility--Illinois, 2005. Clin Infect Dis. 2007 Aug 15;45(4):416–20.

235. Zhu Z, Zhang Y, Xu S, Yu P, Tian X, Wang L, et al. Outbreak of acute respiratory disease in China caused by B2 species of adenovirus type 11. J Clin Microbiol. 2009 Mar;47(3):697–703.

236. WHO informal consultation on surveillance of respiratory syncytial virus on the WHO Global Influenza Surveillance and Response System (GISRS) platform, 25–27 March 2015, Geneva, Switzerland [Internet]. Vol. 91, Releve epidemiologique hebdomadaire. Wkly Epidemiol Rec; 2016 [cited 2021 Jan 13]. Available from: https://pubmed.ncbi.nlm.nih.gov/26753193/

237. Schweitzer JW, Justice NA. Respiratory Syncytial Virus Infection. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 [cited 2021 Jan 20]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK459215/

238. Branche AR, Falsey AR. Parainfluenza Virus Infection. Semin Respir Crit Care Med. 2016 Aug;37(4):538–54.

239. Farahmand M, Malekshahi SS, Jabbari MR, Shayestehpour M. The landscape of extrapulmonary manifestations of human parainfluenza viruses: A systematic narrative review. Microbiology and Immunology. 2021;65(1):1–9.

240. Kunz AN, Ottolini M. The Role of Adenovirus in Respiratory Tract Infections. Curr Infect Dis Rep. 2010;12(2):81–7.

241. Usman N, Suarez M. Adenoviruses. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 [cited 2021 Jan 20]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK559072/

242. Turner RB. The Common Cold. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 2015;748-752.e2.

243. Flores AR, Caserta MT. Pharyngitis. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 2015;753-759.e2.

244. Danishyar A, Ashurst JV. Acute Otitis Media. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 [cited 2021 Jan 19]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK470332/

245. Borchers AT, Chang C, Gershwin ME, Gershwin LJ. Respiratory Syncytial Virus—A Comprehensive Review. Clinic Rev Allerg Immunol. 2013 Dec 1;45(3):331–79.

246. Fitzner J, Qasmieh S, Mounts AW, Alexander B, Besselaar T, Briand S, et al. Revision of clinical case definitions: influenza-like illness and severe acute respiratory infection. Bull World Health Organ. 2018 Feb 1;96(2):122–8.

247. Stellrecht KA. Chapter 11 - Molecular Testing for Respiratory Viruses. In: Coleman WB, Tsongalis GJ, editors. Diagnostic Molecular Pathology [Internet]. Academic Press; 2017 [cited 2021 Jan 19]. p. 123–37. Available from: http://www.sciencedirect.com/science/article/pii/B978012800886700011X

248. Sizar O, Carr B. Croup. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 [cited 2021 Jan 19]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK431070/

249. Johnson DW. Croup. BMJ Clin Evid [Internet]. 2014 Sep 29 [cited 2021 Jan 19];2014. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4178284/

250. Denny FW, Murphy TF, Clyde WA, Collier AM, Henderson FW, Senior RS, et al. Croup: An 11-Year Study in a Pediatric Practice. Pediatrics. 1983 Jun 1;71(6):871–6.

251. Griffiths C, Drews SJ, Marchant DJ. Respiratory Syncytial Virus: Infection, Detection, and New Options for Prevention and Treatment. Clin Microbiol Rev. 2017 Jan;30(1):277–319.

252. Tsou T-P, Tan B-F, Chang H-Y, Chen W-C, Huang Y-P, Lai C-Y, et al. Community Outbreak of Adenovirus, Taiwan, 2011. Emerg Infect Dis. 2012 Nov;18(11):1825–32.

253. Friedman JN, Rieder MJ, Walton JM. Bronchiolitis: Recommendations for diagnosis, monitoring and management of children one to 24 months of age. Paediatr Child Health. 2014 Nov;19(9):485–91.

254. Silver AH, Nazif JM. Bronchiolitis. Pediatrics in Review. 2019 Nov 1;40(11):568–76.

255. Florin TA, Plint AC, Zorc JJ. Viral bronchiolitis. The Lancet. 2017 Jan 14;389(10065):211–24.

256. Smith DK, Seales S, Budzik C. Respiratory Syncytial Virus Bronchiolitis in Children. AFP. 2017 Jan 15;95(2):94–9.

257. Koo HJ, Lim S, Choe J, Choi S-H, Sung H, Do K-H. Radiographic and CT Features of Viral Pneumonia. RadioGraphics. 2018 May 1;38(3):719–39.

258. Figueiredo LTM. Viral pneumonia: epidemiological, clinical, pathophysiological and therapeutic aspects. Jornal Brasileiro de Pneumologia. 2009 Sep;35(9):899–906.

259. Dandachi D, Rodriguez-Barradas MC. Viral pneumonia: etiologies and treatment. Journal of Investigative Medicine. 2018 Aug 1;66(6):957–65.

260. Cesario TC. Viruses Associated With Pneumonia in Adults. Clin Infect Dis. 2012 Jul 1;55(1):107–13.

261. Rambaud-Althaus C, Althaus F, Genton B, D'Acremont V. Clinical features for diagnosis of pneumonia in children younger than 5 years: a systematic review and meta-analysis. The Lancet Infectious Diseases. 2015 Apr 1;15(4):439–50.

262. Ruuskanen O, Lahti E, Jennings LC, Murdoch DR. Viral pneumonia. Lancet. 2011;377(9773):1264–75.

263. Hakim FA, Tleyjeh IM. Severe adenovirus pneumonia in immunocompetent adults: a case report and review of the literature. Eur J Clin Microbiol Infect Dis. 2008 Feb 1;27(2):153–8.

264. Lion T. Adenovirus Infections in Immunocompetent and Immunocompromised Patients. Clinical Microbiology Reviews. 2014 Jul 1;27(3):441–62.

265. Cederwall S, Påhlman LI. Respiratory adenovirus infections in immunocompetent and immunocompromised adult patients. Epidemiol Infect. 2020 Jan 3;147:e328.

266. WHO. Global Epidemiological Surveillance Standards for Influenza [Internet]. 2013. Available from: https://www.who.int/influenza/surveillance_monitoring/ili_sari_surveillance_case_definition/en/

267. Fitzner J, Qasmieh S, Mounts AW, Alexander B, Besselaar T, Briand S, et al. Revision of clinical case definitions: influenza-like illness and severe acute respiratory infection. Bull World Health Organ. 2018 Feb 1;96(2):122–8.

268. Chow EJ, Doyle JD, Uyeki TM. Influenza virus-related critical illness: prevention, diagnosis, treatment. Crit Care [Internet]. 2019 Jun 12 [cited 2021 Jan 21];23. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6563376/

269. Alroy KA, Do TT, Tran PD, Dang TQ, Vu LN, Le NTH, et al. Expanding severe acute respiratory infection (SARI) surveillance beyond influenza: The process and data from 1 year of implementation in Vietnam. Influenza Other Respir Viruses. 2018 Sep;12(5):632–42.

270. Legand A, Briand S, Shindo N, Brooks WA, de Jong MD, Farrar J, et al. Addressing the public health burden of respiratory viruses: the Battle against Respiratory Viruses (BRaVe) Initiative. Future Virology. 2013 Sep 16;8(10):953–68.

271. Zhang N, Wang L, Deng X, Liang R, Su M, He C, et al. Recent advances in the detection of respiratory virus infection in humans. J Med Virol. 2020 Apr;92(4):408–17.

272. Sadeghi CD, Aebi C, Gorgievski-Hrisoho M, Mühlemann K, Barbani MT. Twelve years' detection of respiratory viruses by immunofluorescence in hospitalised children: impact of the introduction of a new respiratory picornavirus assay. BMC Infectious Diseases. 2011 Feb 7;11(1):41.

273. Basile K, Kok J, Dwyer DE. Point-of-care diagnostics for respiratory viral infections. Expert Rev Mol Diagn. 2017 Dec 26;18(1):75–83.

274. Kim H, Chung D-R, Kang M. A new point-of-care test for the diagnosis of infectious diseases based on multiplex lateral flow immunoassays. Analyst. 2019 Apr 8;144(8):2460–6.

275. Slinger R, Milk R, Gaboury I, Diaz-Mitoma F. Evaluation of the QuickLab RSV Test, a New Rapid Lateral-Flow Immunoassay for Detection of Respiratory Syncytial Virus Antigen. J Clin Microbiol. 2004 Aug;42(8):3731–3.

276. Liolios L, Jenney A, Spelman D, Kotsimbos T, Catton M, Wesselingh S. Comparison of a Multiplex Reverse Transcription-PCR-Enzyme Hybridization Assay with Conventional Viral Culture and Immunofluorescence Techniques for the Detection of Seven Viral Respiratory Pathogens. J Clin Microbiol. 2001 Aug;39(8):2779–83.

277. Bentzen EL, House F, Utley TJ, Crowe JE, Wright DW. Progression of respiratory syncytial virus infection monitored by fluorescent quantum dot probes. Nano Lett. 2005 Apr;5(4):591–5.

278. Tripp RA, Alvarez R, Anderson B, Jones L, Weeks C, Chen W. Bioconjugated nanoparticle detection of respiratory syncytial virus infection. Int J Nanomedicine. 2007 Mar;2(1):117–24.

279. Mahony JB, Petrich A, Smieja M. Molecular diagnosis of respiratory virus infections. Critical Reviews in Clinical Laboratory Sciences. 2011 Dec 1;48(5–6):217–49.

280. Wu W, Tang Y-W. Emerging Molecular Assays for Detection and Characterization of Respiratory Viruses. Clinics in Laboratory Medicine. 2009 Dec 1;29(4):673–93.

281. Mahony JB. Nucleic acid amplification-based diagnosis of respiratory virus infections. Expert Review of Anti-infective Therapy. 2010 Nov 1;8(11):1273–92.

282. Nelson PP, Rath BA, Fragkou PC, Antalis E, Tsiodras S, Skevaki C. Current and Future Point-of-Care Tests for Emerging and New Respiratory Viruses and Future Perspectives. Front Cell Infect Microbiol [Internet]. 2020 Apr 29 [cited 2021 Jan 25];10. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7202255/

283. Sanger F, Nicklen S, Coulson AR. DNA sequencing with chain-terminating inhibitors. Proc Natl Acad Sci U S A. 1977 Dec;74(12):5463–7.

284. Goya S, Valinotto LE, Tittarelli E, Rojo GL, Nabaes Jodar MS, Greninger AL, et al. An optimized methodology for whole genome sequencing of RNA respiratory viruses from nasopharyngeal aspirates. PLoS One [Internet]. 2018 Jun 25 [cited 2021 Jan 25];13(6). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6016902/

285. Seto WH, Conly JM, Pessoa-Silva CL, Malik M, Eremin S. Infection prevention and control measures for acute respiratory infections in healthcare settings: an update. East Mediterr Health J. 2013;19 Suppl 1:S39-47.

286. Jefferson T, Mar CBD, Dooley L, Ferroni E, Al-Ansary LA, Bawazeer GA, et al. Physical interventions to interrupt or reduce the spread of respiratory viruses. Cochrane Database of Systematic Reviews [Internet]. 2011 [cited 2019 Oct 21];(7). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD006207.pub4/full

287. Luby SP, Agboatwalla M, Feikin DR, Painter J, Billhimer W, Altaf A, et al. Effect of handwashing on child health: a randomised controlled trial. The Lancet. 2005 Jul 16;366(9481):225–33.

288. Papadopoulos NG, Megremis S, Kitsioulis NA, Vangelatou O, West P, Xepapadaki P. Promising approaches for the treatment and prevention of viral respiratory illnesses. Journal of Allergy and Clinical Immunology. 2017 Oct 1;140(4):921–32.

289. Ruckwardt TJ, Morabito KM, Graham BS. Immunological Lessons from Respiratory Syncytial Virus Vaccine Development. Immunity. 2019 Sep 17;51(3):429–42.

290. Simões EAF, Bont L, Manzoni P, Fauroux B, Paes B, Figueras-Aloy J, et al. Past, Present and Future Approaches to the Prevention and Treatment of Respiratory Syncytial Virus Infection in Children. Infect Dis Ther. 2018 Mar 1;7(1):87–120.

291. Groothuis JR, Simoes EA, Levin MJ, Hall CB, Long CE, Rodriguez WJ, et al. Prophylactic administration of respiratory syncytial virus immune globulin to high-risk infants and young children. The Respiratory Syncytial Virus Immune Globulin Study Group. N Engl J Med. 1993 Nov 18;329(21):1524–30.

292. Graham BS. Vaccine development for respiratory syncytial virus. Curr Opin Virol. 2017 Apr;23:107–12.

293. Higgins D, Trujillo C, Keech C. Advances in RSV vaccine research and development – A global agenda. Vaccine. 2016 Jun 3;34(26):2870–5.

294. Simões E, Bont L, Manzoni P, Fauroux B, Paes B, Figueras-Aloy J, et al. Past, Present and Future Approaches to the Prevention and Treatment of Respiratory Syncytial Virus Infection in Children. Infectious Diseases and Therapy. 2018 Feb 22;7.

295. Garg R, Brownlie R, Latimer L, Gerdts V, Potter A, van Drunen Littel-van den Hurk S. A chimeric glycoprotein formulated with a combination adjuvant induces protective immunity against both human respiratory syncytial virus and parainfluenza virus type 3. Antiviral Research. 2018 Oct 1;158:78–87.

296. Eveno T, Dirr L, El-Deeb IM, Guillon P, von Itzstein M. Targeting Human Parainfluenza Virus Type-1 Haemagglutinin-Neuraminidase with Mechanism-Based Inhibitors. Viruses

[Internet]. 2019 May 5 [cited 2021 Jan 22];11(5). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6563277/

297. Bayon J-CL, Lina B, Rosa-Calatrava M, Boivin G. Recent developments with live-attenuated recombinant paramyxovirus vaccines. Reviews in Medical Virology. 2013;23(1):15–34.

298. Lynch JP, Kajon AE. Adenovirus: Epidemiology, Global Spread of Novel Serotypes, and Advances in Treatment and Prevention. Semin Respir Crit Care Med. 2016 Aug;37(4):586–602.

299. Kuschner RA, Russell KL, Abuja M, Bauer KM, Faix DJ, Hait H, et al. A phase 3, randomized, double-blind, placebo-controlled study of the safety and efficacy of the live, oral adenovirus type 4 and type 7 vaccine, in U.S. military recruits. Vaccine. 2013 Jun 19;31(28):2963–71.

300. Chen S, Tian X. Vaccine development for human mastadenovirus. J Thorac Dis. 2018 Jul;10(Suppl 19):S2280–94.

301. Gray GC. Adenovirus 4 and 7 Vaccine: New Body Armor for U.S. Marine Corps Officer Trainees. J Infect Dis [Internet]. [cited 2019 Oct 21]; Available from: https://academic.oup.com/jid/advance-article/doi/10.1093/infdis/jiz061/5308337

302. Tian X, Jiang Z, Fan Y, Qiu S, Zhang L, Li X, et al. A tetravalent vaccine comprising hexon-chimeric adenoviruses elicits balanced protective immunity against human adenovirus types 3, 7, 14 and 55. Antiviral Research. 2018 Jun 1;154:17–25.

303. Liu T, Zhou Z, Tian X, Liu W, Xu D, Fan Y, et al. A recombinant trivalent vaccine candidate against human adenovirus types 3, 7, and 55. Vaccine. 2018 Apr 12;36(16):2199–206.

304. Brendish NJ, Clark TW. Antiviral treatment of severe non-influenza respiratory virus infection. Curr Opin Infect Dis. 2017 Dec;30(6):573–8.

305. Tal G, Cesar K, Oron A, Houri S, Ballin A, Mandelberg A. Hypertonic saline/epinephrine treatment in hospitalized infants with viral bronchiolitis reduces hospitalization stay: 2 years experience. Isr Med Assoc J. 2006 Mar;8(3):169–73.

306. Gross AE, Bryson ML. Oral Ribavirin for the Treatment of Noninfluenza Respiratory Viral Infections: A Systematic Review. Ann Pharmacother. 2015 Oct 1;49(10):1125–35.

307. Kalergis AM, Soto JA, Gálvez NMS, Andrade CA, Fernandez A, Bohmwald K, et al. Pharmacological management of human respiratory syncytial virus infection. Expert Opin Pharmacother. 2020 Dec;21(18):2293–303.

308. Griffiths C, Drews SJ, Marchant DJ. Respiratory Syncytial Virus: Infection, Detection, and New Options for Prevention and Treatment. Clin Microbiol Rev. 2017 Jan;30(1):277–319.

309. Mazur NI, Martinón-Torres F, Baraldi E, Fauroux B, Greenough A, Heikkinen T, et al. Lower respiratory tract infection caused by respiratory syncytial virus: current management and new therapeutics. The Lancet Respiratory Medicine. 2015 Nov 1;3(11):888–900.

310. Behzadi MA, Leyva-Grado VH. Overview of Current Therapeutics and Novel Candidates Against Influenza, Respiratory Syncytial Virus, and Middle East Respiratory Syndrome Coronavirus Infections. Front Microbiol [Internet]. 2019 Jun 19 [cited 2021 Jan 23];10. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6594388/

311. Chibanga VP, Dirr L, Guillon P, El-Deeb IM, Bailly B, Thomson RJ, et al. New antiviral approaches for human parainfluenza: Inhibiting the haemagglutinin-neuraminidase. Antiviral Research. 2019 Jul 1;167:89–97.

312. Coleman KK, Wong CC, Jayakumar J, Nguyen TT, Wong AWL, Yadana S, et al. Adenoviral Infections in Singapore: Should New Antiviral Therapies and Vaccines Be Adopted? J Infect Dis [Internet]. [cited 2019 Oct 21]; Available from: https://academic.oup.com/jid/advance-article/doi/10.1093/infdis/jiz489/5576003

313. Wold WSM, Tollefson AE, Ying B, Spencer JF, Toth K. Drug development against human adenoviruses and its advancement by Syrian hamster models. FEMS Microbiol Rev. 2019 Jul 1;43(4):380–8.

314. Meena JP, Phillips RS, Kinsey S. Brincidofovir as a Salvage Therapy in Controlling Adenoviremia in Pediatric Recipients of Hematopoietic Stem Cell Transplant. Journal of Pediatric Hematology/Oncology. 2019 Oct;41(7):e467.

315. MacPherson DW, Gushulak BD, Macdonald L. Health and foreign policy: influences of migration and population mobility. Bull World Health Organ. 2007 Mar;85(3):200–6.

316. Kenya [Internet]. Institute for Health Metrics and Evaluation. 2015 [cited 2021 May 24]. Available from: http://www.healthdata.org/kenya

317. Uganda [Internet]. Institute for Health Metrics and Evaluation. 2015 [cited 2021 May 24]. Available from: http://www.healthdata.org/uganda

318. Tanzania [Internet]. Institute for Health Metrics and Evaluation. 2015 [cited 2021 May 24]. Available from: http://www.healthdata.org/tanzania

319. South Sudan [Internet]. Institute for Health Metrics and Evaluation. 2015 [cited 2021 May 24]. Available from: http://www.healthdata.org/south-sudan

320. Rwanda [Internet]. Institute for Health Metrics and Evaluation. 2015 [cited 2021 May 24]. Available from: http://www.healthdata.org/rwanda

321. Burundi [Internet]. Institute for Health Metrics and Evaluation. 2015 [cited 2021 May 24]. Available from: http://www.healthdata.org/burundi

322. Where is Kenya in the World? [Internet]. [cited 2021 Apr 22]. Available from: https://worldpopulationreview.com/country-locations/where-is-kenya

323. Odhiambo EA. Geographic Classification and Geo-coding in Kenya. :24.

324. The Independent Electoral and Boundaries Commission. The Revised Preliminary Report of the Proposed Boundaries of Constituencies and Wards [Internet]. 2012 p. 9–12. Available from: https://www.iebc.or.ke/uploads/resources/WHXao7x83D.pdf

325. Trizer M. 2019 Kenya Population and Housing Census Results [Internet]. Kenya National Bureau of Statistics. 2019 [cited 2020 Oct 8]. Available from: https://www.knbs.or.ke/?p=5621

326. Vos T, Lim SS, Abbafati C, Abbas KM, Abbasi M, Abbasifard M, et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. The Lancet. 2020 Oct 17;396(10258):1204–22.

327. Gichaba M. Relief, Physiography and Drainage. In: Developments in Earth Surface Processes. 2013. p. 23–30.

328. Beck HE, Zimmermann NE, McVicar TR, Vergopolan N, Berg A, Wood EF. Present and future Köppen-Geiger climate classification maps at 1-km resolution. Scientific Data. 2018 Oct 30;5(1):1–12.

329. Ayugi B, Wen W, Chepkemoi D. Analysis of Spatial and Temporal Patterns of Rainfall Variations over Kenya. Environmental Earth Sciences. 2016 Dec 2;6:69–83.

330. Wakachala F, Shilenje ZW, Nguyo J, Shaka S, Apondo W, Rehmani MIA, et al. Statistical Patterns of Rainfall Variability in the Great Rift Valley of Kenya. Journal of Environmental and Agricultural Sciences 2313-8629. 2015 Oct 7;5:17–26.

331. Recha C, Shisanya C, Traore P, Makokha G, Lodoun T, A. S. Determination of seasonal rainfall variability, onset and cessation in semi-arid Tharaka district, Kenya. Theoretical and Applied Climatology. 2011 May 1;108.

332. Marigi S, Njogu A, Githungo W. Trends of Extreme Temperature and Rainfall Indices for Arid and Semi-Arid Lands of South Eastern Kenya. Journal of Geoscience and Environment Protection. 2016 Jan 1;04:158–71.

333. Mutua M. Annual and Seasonal Rainfall Variability for the Kenyan Highlands from 1900-2012. 2020 Sep 11;

334. Makokha G, Shisanya C. Trends in Mean Annual Minimum and Maximum Near Surface Temperature in Nairobi City, Kenya. Advances in Meteorology. 2010 Mar 2;2010.

335. Ziegler T, Mamahit A, Cox NJ. 65 years of influenza surveillance by a World Health Organization-coordinated global network. Influenza Other Respir Viruses. 2018 Sep;12(5):558–65.

336. Hay AJ, McCauley JW. The WHO global influenza surveillance and response system (GISRS)-A future perspective. Influenza Other Respir Viruses. 2018 Sep;12(5):551–7.

337. Radin JM, Katz MA, Tempia S, Talla Nzussouo N, Davis R, Duque J, et al. Influenza surveillance in 15 countries in Africa, 2006-2010. J Infect Dis. 2012 Dec 15;206 Suppl 1:S14-21.

338. Sims LD, Domenech J, Benigno C, Kahn S, Kamata A, Lubroth J, et al. Origin and evolution of highly pathogenic H5N1 avian influenza in Asia. Vet Rec. 2005 Aug 6;157(6):159–64.

339. Michael Thrusfield. Veterinary Epidemiology [Internet]. Third Edition. Veterinary Clinical Studies Royal (Dick) School of Veterinary Studies University of Edinburgh: Blackwell Science Ltd, a Blackwell Publishing company; 2005. 232–233 p. Available from: https://www.wiley.com/en-au/Veterinary+Epidemiology%2C+3rd+Edition-p-9781118713419

340. Dahoo I, Wayne M, Stryhn H. Veterinary Epidemiology Research. 2003.

341. Central Bureau of Statistics-Minstry of Finance and Planning. Analytical Report on Population Projections VII: Kenya 1999 population and housing census. 2002 p. 32.

342. Analytical report on population projection 2010-2030 [Internet]. Available from: https://www.knbs.or.ke/?page_id=3142

343. Google Earth Pro 7.3.3.7786 (64-bit) [Internet]. Kenya. -0.023559°Lat, 37.906193°Long, Eye Alt 1479.70.: Data SIO,NOAA. US. Navy, NGA, GEBCO; 2020. Available from: https://www.google.com/earth/index.html

344. Wan Z, Zhang Y, Zhang Q, Li Z. Validation of the land-surface temperature products retrieved from Terra Moderate Resolution Imaging Spectroradiometer data. Remote Sensing of Environment. 2002 Nov 1;83(1):163–80.

345. Novella NS, Thiaw WM. African Rainfall Climatology Version 2 for Famine Early Warning Systems. J Appl Meteor Climatol. 2013 Mar 1;52(3):588–606.

346. Willmott, C. J., K. Matsuura. Download Data Archives [Internet]. 2001 [cited 2020 Aug 6]. Available from: http://climate.geog.udel.edu/~climate/html_pages/download.html#T2017

347. United Nations Office for the Coordination of Humanitarian Affairs. Kenya - Subnational Administrative Boundaries [Internet]. The Humanitarian Data Exchange (HDX). 2021 [cited 2021 May 12]. Available from: https://data.humdata.org/dataset/ken-administrative-boundaries

348. Kenmoe S, Bigna JJ, Well EA, Simo FBN, Penlap VB, Vabret A, et al. Prevalence of human respiratory syncytial virus infection in people with acute respiratory tract infections in Africa: A systematic review and meta-analysis. Influenza Other Respir Viruses. 2018 Nov;12(6):793–803.

349. Lefebvre A, Manoha C, Bour J-B, Abbas R, Fournel I, Tiv M, et al. Human metapneumovirus in patients hospitalized with acute respiratory infections: A meta-analysis. J Clin Virol. 2016 Aug;81:68–77.

350. Hoy D, Brooks P, Woolf A, Blyth F, March L, Bain C, et al. Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. J Clin Epidemiol. 2012 Sep;65(9):934–9.

351. Shamliyan T, Kane RL, Dickinson S. A systematic review of tools used to assess the quality of observational studies that examine incidence or prevalence and risk factors for diseases. J Clin Epidemiol. 2010 Oct;63(10):1061–70.

352. Nyaga VN, Arbyn M, Aerts M. Metaprop: a Stata command to perform meta-analysis of binomial data. Archives of Public Health. 2014 Nov 10;72(1):39.

353. Barendregt JJ, Doi SA, Lee YY, Norman RE, Vos T. Meta-analysis of prevalence. J Epidemiol Community Health. 2013 Nov 1;67(11):974–8.

354. Brockwell SE, Gordon IR. A comparison of statistical methods for meta-analysis. Stat Med. 2001 Mar 30;20(6):825–40.

355. DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled Clinical Trials. 1986 Sep 1;7(3):177–88.

356. Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods. Stat Med. 1998 Apr 30;17(8):857–72.

357. B.Sc.[1] MH, Cuijpers[2] PDP, Furukawa[3] PDTA, Ebert[2] APDDD. Chapter 6 Between-study Heterogeneity | Doing Meta-Analysis in R [Internet]. [cited 2019 Sep 24]. Available from: https://bookdown.org/MathiasHarrer/Doing_Meta_Analysis_in_R/heterogeneity.html

358. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003 Sep 6;327(7414):557–60.

359. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002 Jun 15;21(11):1539–58.

360. metametabias.pdf [Internet]. [cited 2019 Sep 24]. Available from: https://www.stata.com/manuals/metametabias.pdf

361. Lin L, Chu H, Murad MH, Hong C, Qu Z, Cole SR, et al. Empirical Comparison of Publication Bias Tests in Meta-Analysis. J GEN INTERN MED. 2018 Aug 1;33(8):1260–7.

362. Shi X, Nie C, Shi S, Wang T, Yang H, Zhou Y, et al. Effect comparison between Egger's test and Begg's test in publication bias diagnosis in meta-analyses: evidence from a pilot survey. Int J Res Stud Biosci. 2017;5(5):14–20.

363. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997 Sep 13;315(7109):629–34.

364. World Health Organization, Global Influenza Programme, University of Edinburgh, World Health Organization. A manual for estimating disease burden associated with seasonal influenza [Internet]. 2015 [cited 2019 Nov 25]. Available from: http://apps.who.int/iris/bitstream/10665/178801/1/9789241549301_eng.pdf?ua=1

365. Bloomfield P. Fourier Analysis of Time Series: An Introduction. John Wiley & Sons; 2004. 285 p.

366. Hogan AB, Anderssen RS, Davis S, Moore HC, Lim FJ, Fathima P, et al. Time series analysis of RSV and bronchiolitis seasonality in temperate and tropical Western Australia. Epidemics. 2016 Sep 1;16:49–55.

367. Hosmer D.W, Lemeshow, S. Applied Logistic Regression. 2nd edn. 2000.

368. Choi M. Book Review: Spatial Analysis in Epidemiology. Healthc Inform Res. 2013 Jun;19(2):148–9.

369. Guidoum AC. Kernel Estimator and Bandwidth Selection for Density and its Derivatives. :22.

370. Oxoli D, Prestifilippo G, Bertocchi D, Zurbarán M. Enabling spatial autocorrelation mapping in QGIS: The hotspot analysis Plugin. Geoingegneria Ambientale e Mineraria. 2017 Aug 1;151:45–50.

371. Anselin L. Local Indicators of Spatial Association—LISA. Geographical Analysis. 1995;27(2):93–115.

372. Robertson C, Nelson TA, MacNab YC, Lawson AB. Review of methods for space–time disease surveillance. Spat Spatiotemporal Epidemiol. 2010 Jul;1(2):105–16.

373. Oxoli D, Molinari M, Brovelli M. Hotspot Analysis, an open source GIS tool for exploratory spatial data analysis: application to the study of soil consumption in Italy. Rendiconti Online della Società Geologica Italiana. 2018 Nov 1;46:82–7.

374. Vilinová K. Spatial Autocorrelation of Breast and Prostate Cancer in Slovakia. Int J Environ Res Public Health [Internet]. 2020 Jun [cited 2021 Mar 1];17(12). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7344400/

375. Kulldorff M, Heffernan R, Hartman J, Assunção R, Mostashari F. A Space–Time Permutation Scan Statistic for Disease Outbreak Detection. PLOS Medicine. 2005 Feb 15;2(3):e59.

376. Kulldorff M. A spatial scan statistic. Communications in Statistics - Theory and Methods. 1997 Jan 1;26(6):1481–96.

377. Sanchez JL, Johns MC, Burke RL, Vest KG, Fukuda MM, Yoon I-K, et al. Capacity-building efforts by the AFHSC-GEIS program. BMC Public Health. 2011 Mar 4;11(2):S4.

378. Nyatanyi T, Nkunda R, Rukelibuga J, Palekar R, Muhimpundu MA, Kabeja A, et al. Influenza sentinel surveillance in Rwanda, 2008-2010. J Infect Dis. 2012 Dec 15;206 Suppl 1:S74-79.

379. Sanicas M, Forleo E, Pozzi G, Diop D. A review of the surveillance systems of influenza in selected countries in the tropical region. Pan Afr Med J [Internet]. 2014 Oct 1 [cited 2018 Oct 31];19. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4341259/

380. Kenmoe S, Bigna JJ, Well EA, Simo FBN, Penlap VB, Vabret A, et al. Prevalence of human respiratory syncytial virus infection in people with acute respiratory tract infections in Africa: A systematic review and meta-analysis. Influenza Other Respir Viruses. 2018 Jun 16;

381. Zhang Y, Yuan L, Zhang Y, Zhang X, Zheng M, Kyaw MH. Burden of respiratory syncytial virus infections in China: Systematic review and meta-analysis. J Glob Health. 2015 Dec;5(2):020417.

382. Njouom R, Yekwa EL, Cappy P, Vabret A, Boisier P, Rousset D. Viral etiology of influenza-like illnesses in Cameroon, January-December 2009. J Infect Dis. 2012 Dec 15;206 Suppl 1:S29-35.

383. Villaran MV, García J, Gomez J, Arango AE, Gonzales M, Chicaiza W, et al. Human parainfluenza virus in patients with influenza-like illness from Central and South America during 2006–2010. Influenza Other Respir Viruses. 2014 Mar;8(2):217–27.

384. Feng L, Li Z, Zhao S, Nair H, Lai S, Xu W, et al. Viral Etiologies of Hospitalized Acute Lower Respiratory Infection Patients in China, 2009-2013. PLOS ONE. 2014 Jun 19;9(6):e99419.

385. Daniel R. Feikin, M. Kariuki Njenga, Godfrey Bigogo, Barrack Aura, George Aol, Allan Audi, et al. Etiology and Incidence of viral and bacterial acute respiratory illness among older children and adults in rural western Kenya, 2007-2010. PLoS ONE. 2012;7(8):e43656.

386. Horton KC, Dueger EL, Kandeel A, Abdallat M, El-Kholy A, Al-Awaidy S, et al. Viral etiology, seasonality and severity of hospitalized patients with severe acute respiratory infections in the Eastern Mediterranean Region, 2007-2014. PLoS ONE. 2017;12(7):e0180954.

387. Niang MN, Diop NS, Fall A, Kiori DE, Sarr FD, Sy S, et al. Respiratory viruses in patients with influenza-like illness in Senegal: Focus on human respiratory adenoviruses. PLoS ONE. 2017;12(3):e0174287.

388. Biggs HM, Lu X, Dettinger L, Sakthivel S, Watson JT, Boktor SW. Adenovirus-Associated Influenza-Like Illness among College Students, Pennsylvania, USA. Emerg Infect Dis. 2018 Nov;24(11):2117–9.

389. Malhotra B, Swamy MA, Janardhan Reddy PV, Gupta ML. Viruses causing severe acute respiratory infections (SARI) in children ≤5 years of age at a tertiary care hospital in Rajasthan, India. Indian J Med Res. 2016 Dec;144(6):877–85.

390. Munywoki PK, Koech DC, Agoti CN, Lewa C, Cane PA, Medley GF, et al. The source of respiratory syncytial virus infection in infants: a household cohort study in rural Kenya. J Infect Dis. 2014 Jun 1;209(11):1685–92.

391. Weber A, Weber M, Milligan P. Modeling epidemics caused by respiratory syncytial virus (RSV). Math Biosci. 2001 Aug;172(2):95–113.

392. Murray EL, Klein M, Brondi L, McGOWAN JE, Mels CV, Brooks WA, et al. Rainfall, household crowding, and acute respiratory infections in the tropics. Epidemiology & Infection. 2012 Jan;140(1):78–86.

393. Nyoka R, Omony J, Mwalili SM, Achia TNO, Gichangi A, Mwambi H. Effect of climate on incidence of respiratory syncytial virus infections in a refugee camp in Kenya: A non-Gaussian time-series analysis. PLOS ONE. 2017 Jun 1;12(6):e0178323.

394. Suryadevara M, Domachowske JB. Epidemiology and Seasonality of Childhood Respiratory Syncytial Virus Infections in the Tropics. Viruses. 2021 Apr;13(4):696.

395. Gamba-Sanchez N, Rodriguez-Martinez CE, Sossa-Briceño MP. Epidemic activity of respiratory syncytial virus is related to temperature and rainfall in equatorial tropical countries. Epidemiol Infect. 2016 Jul;144(10):2057–63.

396. Rodriguez-Martinez CE, Sossa-Briceño MP, Acuña-Cordero R. Relationship between meteorological conditions and respiratory syncytial virus in a tropical country. Epidemiol Infect. 2015 Sep;143(12):2679–86.

397. Umuhoza T, Bulimo WD, Oyugi J, Schnabel D, Mancuso JD. Prevalence and factors influencing the distribution of influenza viruses in Kenya: Seven-year hospital-based surveillance of influenza-like illness (2007–2013). PLOS ONE. 2020 Aug 21;15(8):e0237857.

398. Murray EL, Klein M, Brondi L, McGOWAN JE, Mels CV, Brooks WA, et al. Rainfall, household crowding, and acute respiratory infections in the tropics. Epidemiology & Infection. 2012 Jan;140(1):78–86.

399. Umuhoza T, Oyugi J, Mancuso JD, Ahmed A, Bulimo WD. Morbidity burden, seasonality and factors associated with the human respiratory syncytial virus, human parainfluenza virus, and human adenovirus infections in Kenya. IJID Regions. 2021 Dec 1;1:72–8.

400. O'Meara WP, Mott JA, Laktabai J, Wamburu K, Fields B, Armstrong J, et al. Etiology of pediatric fever in western Kenya: a case-control study of falciparum malaria, respiratory viruses, and streptococcal pharyngitis. Am J Trop Med Hyg. 2015 May;92(5):1030–7.

401. Feikin DR, Njenga MK, Bigogo G, Aura B, Aol G, Audi A, et al. Etiology and Incidence of Viral and Bacterial Acute Respiratory Illness among Older Children and Adults in Rural Western Kenya, 2007–2010. PLOS ONE. 2012 Aug 24;7(8):e43656.

402. Mbui FM, Achilla RA, Coldren RL, Bulimo WD. Serotype Diversity of Respiratory Human Adenoviruses amongst Pediatric Patients from Western Kenya, 2010-2012. African Journal of Pharmacology and Therapeutics [Internet]. 2016 Oct 17 [cited 2021 Jul 26];5(3). Available from: http://journals.uonbi.ac.ke/ajpt/article/view/1521

403. Achilla R, Bulimo W, Schnabel D. An Evaluation of the Epidemiology of Adenovirus Infections in Kenya Using a Sustained Laboratory-Based Sentinel Surveillance System. International Journal of Infectious Diseases. 2008 Dec 1;12:e303–4.

404. Pang J, Jin J, Loh JP, Tan BH, Koh WHV, Ng SH, et al. Risk factors for febrile respiratory illness and mono-viral infections in a semi-closed military environment: a case-control study. BMC Infectious Diseases. 2015 Jul 25;15:288.

405. Walls T, Shankar AG, Shingadia D. Adenovirus: an increasingly important pathogen in paediatric bone marrow transplant patients. Lancet Infect Dis. 2003 Feb;3(2):79–86.

406. Tango T, Takahashi K. A flexible spatial scan statistic with a restricted likelihood ratio for detecting disease clusters. Stat Med. 2012 Dec 30;31(30):4207–18.

407. Kulldorff M. A spatial scan statistic. Communications in Statistics - Theory and Methods. 1997 Jan 1;26(6):1481–96.

408. Rao H, Shi X, Zhang X. Using the Kulldorff's scan statistical analysis to detect spatio-temporal clusters of tuberculosis in Qinghai Province, China, 2009–2016. BMC Infect Dis [Internet]. 2017 Aug 21 [cited 2020 Nov 19];17. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5563899/

409. Gwitira I, Mukonoweshuro M, Mapako G, Shekede MD, Chirenda J, Mberikunashe J. Spatial and spatio-temporal analysis of malaria cases in Zimbabwe. Infectious Diseases of Poverty. 2020 Oct 22;9(1):146.

ANNEXES

Annex 1: List searched health and research institutions' names

No	Abbreviation	Name	Type	URL	Contact Person	E-mail	Country
1	WHO	World health organization	Non-government organization	http://www.who.int/library/en/	Dr Zabulon Yoti	yotiza@who.int	Regional
2	AMREF	African medical research foundation	Non-government organization	amref.org/home/	NA	NA	Regional
3	KEMRI	Kenya medical research institute	Government institute	https://www.kemri.org/	Samwel Morris L.S.	symolis@gmail.com	Kenya
4	KEMRI-WT	Welcome-Trust	Non-government organization	http://kemri-wellcome.org/all-publication/	James Nokes	JNokes@kemri-wellcome.org	Kenya
5	CDC-K	Center of Diseases control and prevention kenya	Non-government organization	www.cdc.gov/globalhealth/countries/kenya	M. A Widdowson	zux5@cdc.gov	Kenya
6	MoH-K	Ministry of health Kenya	Government institute	http://www.health.go.ke/	NA	NA	Kenya
7	UoN	University of Nairobi	Government institute	http://erepository.uonbi.ac.ke/	Angela Mumo	angela.mumo@uonbi.ac.ke	Kenya
8	KNH	Kenyatta National Hospital	Government institute	http://knh.or.ke/	NA	NA	Kenya

No	Abbreviation	Name	Type	URL	Contact Person	e-mail	Country
9	MOH-U	Ministry of Health Uganda	Government institute	http://health.go.ug/affiliated-institutions	NA	NA	Uganda
10	UNHRO	Uganda National Health Research Organization	Government institute	http://unhro.org.ug/	Harriet Nabudere	harrietnabudere@yahoo.com	Uganda
11	UVRI	Uganda Virus Research Institute	Government institute	http://www.uvri.go.ug/	Julius Lutwama	jjlutwama03@yahoo.com	Uganda
12	Mak	Makerere University	Government institute	https://www.mak.ac.ug/	Alison Kinengyere	alison.kine@gmail.com	Uganda
13	Mulago	Mulago National referral hospital	Government institute	http://www.mulago.or.ug/	Alison Kinengyere	alison.kine@gmail.com	Uganda
14	MoH-R	Ministry of health Rwanda	Government institute	http://www.moh.gov.rw/index.php?id=5	Muhire Andrew	muhireandrew@gmail.com	Rwanda
15	RBC	Rwanda Biomedical Center	Government institute	http://www.rbc.gov.rw/index.php?id=263	J.P Musabyimana	musajampiereb@gmail.com	Rwanda
16	UR	University of Rwanda	Government institute	http://www.library.ur.ac.rw/	Ella Larrissa Ndoli	ellalarissan@gmail.com	Rwanda
17	MoH-T	Ministry of health Tanzania	Government institute	http://www.mcdgc.go.tz/	Vida MMBAGA	makundiv@yahoo.com	Tanzania

No	Abbreviation	Name	Type	URL	Contact Person	e-mail	Country
18	NIMR	National Institute for Medical Research	Government institute	http://www.nimr.or.tz/	NA	NA	Tanzania
19	MNH	Muhimbili National hospital	Government institute	http://www.mnh.or.tz/	NA	NA	Tanzania
20	MUHAS	Muhimbili University of Health and Allied Sciences	Government institute	library.muhas.ac.tz	NA	NA	Tanzania
21	Minisanté.Bi	Ministère de la santé et lutte contre le SIDA	Government institute	www.minisante.bi	Florence Munezero	+257 79 916 054	Burundi
22	INSP	Institut National de Santé Publique	Government institute	insp.bi	Dionis Nizigiyimana	nizigiyimana.dionis@gmail.com	Burundi
23	UB	Univérisite de Burundi	Government institute	http://www.ub.edu.bi	NA	NA	Burundi
24	ANISE	The African Network for Influenza Surveillance and Epidemiology	Non-government organization	http://www.anise-network.org/	Ndahwouh Talla	Linkedin	International

Annex 2: List of recorded clinical characteristics during ILI surveillance (2007-2013)

Influenza like illness (ILI)	Clinical characteristics
Human respiratory syncytial virus (HRSV) Human parainfluenza (HPIV) Human adenoviruses (HAdV)	Fever
	Cough
	Runny Nose
	Retro-Orbital pain
	Nasal stiffness
	Malaise
	Vomiting
	Fatigue
	Breathing difficulty
	Chills
	Diarrhea
	Headache
	Sore throat
	Abdominal Pain
	Sputum
	Neurological signs
	Joint Pain
	Muscle Aches
	Bleeding

Annex 3: Population per county from 2007 to 2013

County	2007	2008	2009	2010	2011	2012	2013
Bomet	640521.5	649936	724186	745617	773157	801671	831115
Busia	680427	694179	743946	761065	772999	785473	798514
Homa Bay	875978	887226	963794	984293	1006756	1029823	1053465
Isiolo	126374	129055	143294	146567	147928	149345	150817
Kericho	727994.5	736773	758339	768350	796729	826112	856454
Kilifi	1019640	1040543	1109735	1133208	1175021	1218024	1262127
Kisii	1096316	1108567	1152282	1176791	1203648	1231223	1259489
Kisumu	938122	950218	968909	989514	1012102	1035287	1059053
Machakos	1073605	1089193	1098584	1123672	1134005	1144770	1155957
Meru	1298459	1316387	1356301	1387275	1400032	1413323	1427135
Mombasa	849171	870197	939370	959187	994575	1030973	1068307
Nairobi	2940911	3038553	3138369	3144918	3351315	3563473	3781394
Kajiado	550780	568554	687312	701919	727849	754693	782409
Kiambu	1467148	1466463	1623282	1660366	1692651	1726128	1760692
Nyamira	561480	566258	598252	610976	624921	639238	653914

Annex 4: Surveillance site spatial location

No	County	Site	Latitude	Longitude
1	Busia	Alupe	0.496181	34.131329
2	Isiolo	Isiolo	0.354983	37.5840354
3	Kericho	Kericho	-0.41357	34.9298756
4	Kisii	Kisii	-0.69384	34.6447313
5	Kilifi	Malindi	-3.22661	40.1228413
6	Nairobi	Mbagathi	-1.30875	36.8017091
7	Kisumu	New Nyanza	-0.0887	34.7698191
8	Mombasa	Port Reitz	-4.03916	39.5985808

Annex 5: Counties centroids

County	Latutide	Longitude
Bomet	-0.71784	35.29827
Busia	0.38852	34.19271
Homa Bay	-0.54193	34.36145
Isiolo	1.01254	38.54093
Kericho	-0.28882	35.31498
Kilifi	-3.17809	39.68788
Kisii	-0.77435	34.77534
Kisumu	-0.16466	34.83742
Machakos	-1.27738	37.41149
Meru	0.16927	37.76334
Mombasa	-4.01721	39.65465
Nairobi	-1.29091	36.86754
Nyamira	-0.63200	34.96000
Kajiado	-2.11909	36.90885
Kiambu	-1.06725	36.82249

Annex 6: The inclusion and exclusion criteria

Study	Inclusion Criteria	Exclusion Criteria
Human prevalence	Respiratory syncytial virus (RSV), Para-influenza virus (PIV), and adenovirus (HAdV)	Other respiratory viruses
Syndromes	Influenza like illnesses (ILI) and severe acute respiratory illness (SARI)	Other respiratory illness
Publication characteristics	Full article or abstract published in 2007-2020, English language, hospital setting, population in East Africa Community	Case reports, case series, editorials, letters to editors, reviews, commentaries, qualitative studies, studies from countries outside East Africa Community
Study design	Any randomized or non-randomized design	Non-empirical research/modelled data
Outcomes	Prevalence of laboratory-confirmed infections caused HRSVs, HPIVs, and HAdVs	No human prevalence or incidence measure reported

Annex 7: Search strategies

a) Search strategy PubMed database

Search number	Query
21	((((((prevalence[Title/Abstract]) OR ("Prevalence"[Mesh] OR "epidemiology" [Subheading] OR "Cross-Sectional Studies"[Mesh])) OR incidence[Title/Abstract]) OR ("Incidence"[Mesh] OR "epidemiology" [Subheading] OR "Cohort Studies"[Mesh]))) AND ((((((((((acute viral respiratory infection[Title/Abstract]) OR influenza like illness[Title/Abstract]) OR severe acute respiratory illness[Title/Abstract]) OR respiratory syncytial virus[Title/Abstract]) OR ("Respiratory Syncytial Viruses"[Mesh] OR "Respiratory Syncytial Virus Infections"[Mesh] OR "Respiratory Syncytial Virus, Human"[Mesh])) OR parainfluenza virus[Title/Abstract]) OR ("Parainfluenza Virus 5"[Mesh] OR "Parainfluenza Virus 4, Human"[Mesh] OR "Parainfluenza Virus 3, Human"[Mesh] OR "Parainfluenza Virus 2, Human"[Mesh] OR "Parainfluenza Virus 1, Human"[Mesh])) OR adenovirus[Title/Abstract]) OR ("Adenoviridae Infections"[Mesh] OR "Adenovirus Infections, Human"[Mesh] OR "Adenoviruses, Human"[Mesh])) OR other respiratory virus[Title/Abstract]) OR pneumonia[Title/Abstract]) OR ("Pneumonia"[Mesh] OR "Pneumonia, Viral"[Mesh]))) AND ((east african community[Title/Abstract]) OR ((((((Rwanda[Title/Abstract]) OR Burundi) OR Uganda) OR Kenya) OR Tanzania) OR South Sudan)) Filters: from 2007/1/1 - 2020/12/31
20	Search (east african community[Title/Abstract]) OR ((((((Rwanda[Title/Abstract]) OR Burundi) OR Uganda) OR Kenya) OR Tanzania) OR South Sudan)
19	Search ((((((((((acute viral respiratory infection[Title/Abstract]) OR influenza like illness[Title/Abstract]) OR severe acute respiratory illness[Title/Abstract]) OR respiratory syncytial virus[Title/Abstract]) OR ("Respiratory Syncytial Viruses"[Mesh] OR "Respiratory Syncytial Virus Infections"[Mesh] OR "Respiratory Syncytial Virus, Human"[Mesh])) OR parainfluenza virus[Title/Abstract]) OR ("Parainfluenza Virus 5"[Mesh] OR "Parainfluenza Virus 4, Human"[Mesh] OR "Parainfluenza Virus 3, Human"[Mesh] OR "Parainfluenza Virus 2, Human"[Mesh] OR "Parainfluenza Virus 1, Human"[Mesh])) OR adenovirus[Title/Abstract]) OR ("Adenoviridae Infections"[Mesh] OR "Adenovirus Infections, Human"[Mesh] OR "Adenoviruses, Human"[Mesh])) OR other respiratory virus[Title/Abstract]) OR pneumonia[Title/Abstract]) OR ("Pneumonia"[Mesh] OR "Pneumonia, Viral"[Mesh])
18	Search (((prevalence[Title/Abstract]) OR ("Prevalence"[Mesh] OR "epidemiology" [Subheading] OR "Cross-Sectional Studies"[Mesh])) OR incidence[Title/Abstract]) OR ("Incidence"[Mesh] OR "epidemiology" [Subheading] OR "Cohort Studies"[Mesh])
17	Search (((((Rwanda[Title/Abstract]) OR Burundi) OR Uganda) OR Kenya) OR Tanzania) OR South Sudan
16	Search east african community[Title/Abstract]
15	Search "Pneumonia"[Mesh] OR "Pneumonia, Viral"[Mesh]

14	Search pneumonia[Title/Abstract]
13	Search other respiratory virus[Title/Abstract]
12	Search "Adenoviridae Infections"[Mesh] OR "Adenovirus Infections, Human"[Mesh] OR "Adenoviruses, Human"[Mesh]
11	Search adenovirus[Title/Abstract]
10	Search "Parainfluenza Virus 5"[Mesh] OR "Parainfluenza Virus 4, Human"[Mesh] OR "Parainfluenza Virus 3, Human"[Mesh] OR "Parainfluenza Virus 2, Human"[Mesh] OR "Parainfluenza Virus 1, Human"[Mesh]
9	Search parainfluenza virus[Title/Abstract]
8	Search "Respiratory Syncytial Viruses"[Mesh] OR "Respiratory Syncytial Virus Infections"[Mesh] OR "Respiratory Syncytial Virus, Human"[Mesh]
7	Search severe acute respiratory illness[Title/Abstract]
6	Search influenza like illness[Title/Abstract]
5	Search acute viral respiratory infection[Title/Abstract]
4	Search "Incidence"[Mesh] OR "epidemiology" [Subheading] OR "Cohort Studies"[Mesh]
3	Search incidence[Title/Abstract]
2	Search "Prevalence"[Mesh] OR "epidemiology" [Subheading] OR "Cross-Sectional Studies"[Mesh]
1	Search prevalence[Title/Abstract]

b) Search strategy Global Index Medicus database

tw:((tw:(prevalence)) OR (tw:(cross-sectional studies)) OR (tw:(meta-analysis)) OR (tw:(incidence)) OR (tw:(cohort studies)) OR (tw:(epidemiology studies)) AND (tw:(respiratory tract infections)) OR (tw:(upper respiratory tract infections)) OR (tw:(pneumonia, viral)) OR (tw:(respiratory syncytial virus, human)) OR (tw:(parainfluenza virus 1, human)) OR (tw:(parainfluenza virus 2, human)) OR (tw:(parainfluenza virus 3, human)) OR (tw:(adenovirus infections, human)) AND (tw:(africa, eastern)) OR (tw:(kenya)) OR (tw:(tanzania)) OR (tw:(uganda)) OR (tw:(rwanda)) OR (tw:(burundi)) OR (tw:(south sudan))) AND (la:("en")) AND (year_cluster:[2007 TO 2020])

Annex 8: Keywords and MeSH terminologies

No	Key word/Medline	Mesh Synonym/Medline
1	prevalence	Prevalence
		epidemiology sub-heading
		cross-sectional studies
2	incidence	Incidence
		epidemiology sub-heading
		Cohort studies
3	Acute viral respiratory infection	ARTIs
4	influenza like illness	ILI
5	severe acute respiratory infection	SARI
6	respiratory syncytial virus	Respiratory Syncytial Viruses
		Respiratory Syncytial Virus Infections
		Respiratory Syncytial Virus, Human
7	parainfluenza virus	Parainfluenza Virus 5
		Parainfluenza Virus 4,Human
		Parainfluenza Virus 3, Human
		Parainfluenza Virus 2, Human
		Parainfluenza Virus 1, Human
		Paramyxoviridae Infections
8	adenovirus	Adenoviruses, Human
		Adenoviridae Infections
		Adenovirus Infections, Human
9	other respiratory virus	Non Influenza respiratory virus
10	pneumonia	Pneumonia
		Pneumonia, Viral
11	East Africa community	EAC
12	Rwanda	Republic of Rwanda
13	Burundi	Republic of Burundi
14	Kenya	Republic of Kenya
15	Tanzania	Republic of Tanzania
16	Uganda	Republic of Uganda
17	South sudan	Republic of South Sudan

Annex 9: Data extracted from the selected review studies

Title	Author	MM	Year	Country	Age	Syndr-om	Speci-men	Test	Study design	(N)	RSV (n)	RSV (N)	HPIV (n)	HPIV (N)	AdV (n)	AdV (N)
Prevalence of viral aetiologies in children with acute respiratory infections in Nairobi, Kenya	Samwel	4	2009	Kenya	<5	ILI/SARI	OPS	VI	cross-sectional	388	19	388	25	388	27	388
Respiratory Adenovirus Species Circulating In Kenya from 2007-2010	Achilla R et al	36	2012	Kenya	All age	ILI	NPS	IFA	cross-sectional	12959					385	12959
Epidemiology of respiratory viral infections in two long-term refugee camps in Kenya, 2007-2010	Ahmed A.J et al	37	2012	Kenya	All age	ILI/SARI	NPS/OPS	RT-PCR	cross-sectional	6264	781	6264	591	6264	1361	6264

MM (Study period in months), N (overall population), n (positive case), RSV (Respiratory syncytial virus), PIV (Parainfluenza virus), AdV (Adenovirus), VI (Virus isolation), ILI (Influenza like illness), SARI (Severe acute respiratory illness), NPS (Nasal phyrangeal swab), OPS (Oral phyrangeal swab)

Title	Author	MM	Year	Country	Age	Syndr-om	Speci-men	Test	Study design	(N)	RSV (n)	RSV (N)	HPIV (n)	HPIV (N)	AdV (n)	AdV (N)
Surveillance of Human Parainfluenza viruses in Kenya during the 2007-2011 Period	Mitei K et al	46	2012	Kenya		ILI	NPS	IFA	cross-sectional	14990			801	14990		
The viral aetiology of influenza-like illnesses in Kampala and Entebbe, Uganda, 2008	Balinandi S. et al	5	2013	Uganda	All age	ILI	NPS	RT-PCR	cross-sectional	369	12	369	22	369	32	369

MM (Study period in months), N (overall population), n (positive case), RSV (Respiratory syncytial virus), PIV (Parainfluenza virus), AdV (Adenovirus), VI (Virus isolation), ILI (Influenza like illness), SARI (Severe acute respiratory illness), NPS (Nasal phyrangeal swab), OPS (Oral phyrangeal swab)

Title	Author	MM	Year	Country	Age	Syndr-om	Speci-men	Test	Study design	(N)	RSV (n)	RSV (N)	HPIV (n)	HPIV (N)	AdV (n)	AdV (N)
Viral and Bacterial Causes of Severe Acute Respiratory Illness Among Children Aged Less Than 5 Years in a High Malaria Prevalence Area of Western Kenya, 2007–2010	Feikin D.R et al	36	2013	Kenya	<5	SARI	NPS/OPS	RT-PCR	cross-sectional	2497	550	2497			400	2497
The burden of influenza and RSV among inpatients and outpatients in rural western Kenya, 2009-2012	Emukule G.O. et al	36	2014	Kenya	All age	ILI/SARI	NPS/OPS	RT-PCR	cross-sectional	5895	575	5895				

MM (Study period in months), N (overall population), n (positive case), RSV (Respiratory syncytial virus), PIV (Parainfluenza virus), AdV (Adenovirus), VI (Virus isolation), ILI (Influenza like illness), SARI (Severe acute respiratory illness), NPS (Nasal phyrangeal swab), OPS (Oral phyrangeal swab)

Title	Author	MM	Year	Country	Age	Syndr-om	Speci-men	Test	Study design	(N)	RSV (n)	RSV (N)	HPIV (n)	HPIV (N)	AdV (n)	AdV (N)
Prevalence of respiratory viral pathogens in nasopharyngeal and oropharyngeal specimens and clinical outcomes in young children presenting with severe acute respiratory infections at Kenyatta National Hospital	Gachie L.R. et al		2014	Kenya	<5	SARI	NPS/OPS	RT-PCR	cohort	281	54	281	45	281	106	281

MM (Study period in months), N (overall population), n (positive case), RSV (Respiratory syncytial virus), PIV (Parainfluenza virus), AdV (Adenovirus), VI (Virus isolation), ILI (Influenza like illness), SARI (Severe acute respiratory illness), NPS (Nasal phyrangeal swab), OPS (Oral phyrangeal swab)

Title	Author	MM	Year	Country	Age	Syndr-om	Speci-men	Test	Study design	(N)	RSV (n)	RSV (N)	HPIV (n)	HPIV (N)	AdV (n)	AdV (N)
Etiology and Incidence of Viral Acute Respiratory Infections Among Refugees Aged 5 Years and Older in Hagadera Camp, Dadaab, Kenya	Mohamed Gedi A et al	36	2015	Kenya	>=5	ILI/SARI	NPS/OPS	RT-PCR	cross-sectional	419	16	168	24	167	50	167
The Prevalence of Influenza and other Respiratory Viruses among ILI and SARI patients in Tanzania, from January 2016 to August 2017	Mmbaga V. et al		2018	Tanzania		ILI/SARI	NPS/OPS	RT-PCR		257	75	257	26	257	21	257

MM (Study period in months), N (overall population), n (positive case), RSV (Respiratory syncytial virus), PIV (Parainfluenza virus), AdV (Adenovirus), VI (Virus isolation), ILI (Influenza like illness), SARI (Severe acute respiratory illness), NPS (Nasal phyrangeal swab), OPS (Oral phyrangeal swab)

Title	Author	MM	Year	Country	Age	Syndr-om	Speci-men	Test	Study design	(N)	RSV (n)	RSV (N)	HPIV (n)	HPIV (N)	AdV (n)	AdV (N)
The Burden of Influenza and Respiratory Syncytial Virus in Infants 0-2 Months Old in Rural Western Kenya; Preliminary Data, 2015-2017	Nyawanda O.B et al	31	2018	Kenya	<5	ILI	NPS/OPS	RT-PCR	cohort	861	57	861				
Surveillance of respiratory viruses in the outpatient setting in rural coastal Kenya: baseline epidemiological observations	Nyiro J. U et al	12	2018	Kenya	All age	ILI/SARI	NPS	RT-PCR	cross-sectional	5647	219	5647	371	5647	155	5647

MM (Study period in months), N (overall population), n (positive case), RSV (Respiratory syncytial virus), PIV (Parainfluenza virus), AdV (Adenovirus), VI (Virus isolation), ILI (Influenza like illness), SARI (Severe acute respiratory illness), NPS (Nasal phyrangeal swab), OPS (Oral phyrangeal swab)

Annex 10: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Prevalence of human respiratory syncytial virus, parainfluenza and adenoviruses in East Africa Community partner states of Kenya, Tanzania, and Uganda: a systematic review and meta-analysis (2007-2020)	Page 1
ABSTRACT			
Structured summary	2	**Background** Viruses are responsible for a large proportion of acute respiratory tract infections (ARTIs). Human influenza, parainfluenza, respiratory-syncytial-virus, and adenoviruses are among the leading cause of ARTIs. Epidemiological evidence of those respiratory viruses is limited in the East Africa Community (EAC) region. This review sought to identify the prevalence of respiratory syncytial virus, parainfluenza, and adenoviruses among cases of ARTI in the EAC from 2007 to 2020 **Methods** A literature search was conducted in Medline, Global Index Medicus, and the grey literature from public health institutions and programs in the EAC. Two independent reviewers performed data extraction. We used a random effects model to pool the prevalence estimate across studies. We assessed heterogeneity with the I2 statistic, and Cochran's Q test, and further we did subgroup analysis. This review was registered with PROSPERO under registration number CRD42018110186. **Results** A total of 12 studies met the eligibility criteria for the studies documented from 2007 to 2020. The overall pooled prevalence of adenoviruses was 13% (95% confidence interval [CI]: 6-21, N=28829), respiratory syncytial virus 11% (95% CI: 7-15, N=22627), and parainfluenza was 9% (95% CI: 7-11, N= 28363). Pooled prevalence of reported ARTIs, all ages, and locality varied in the included studies. Studies among participants with severe acute respiratory disease had a higher pooled prevalence of all the three viruses. Considerable heterogeneity was noted overall and in subgroup analysis. **Conclusion** Our findings indicate that human adenoviruses, respiratory syncytial virus and parainfluenza virus are prevalent in Kenya, Tanzania, and Uganda. These three respiratory viruses contribute substantially to ARTIs in the EAC, particularly among those with severe disease and those aged five and above.	Page 2-3
INTRODUCTION			

Rationale	3	Acute respiratory tract infections (ARTIs) are among the five most common causes of morbidity and mortality globally, accounting for approximately 3.9 million deaths annually. Most of these deaths occur among young children in developing countries [1]. Viruses are responsible for a large proportion of ARTIs and these are associated with various syndromes of the upper and lower respiratory tract, including: acute otitis media, croup, pneumonia, bronchiolitis, and asthma [2,3]. Additionally, co-infections of viruses and bacteria are commonly reported in severe cases of ARTIs [4,5]. Although viral aetiologies are associated with a large percentage of acute respiratory tract infections, it is difficult to link specific viral agents to a specific syndrome. This is due to the complexity and broad spectrum of illnesses caused by these pathogens. Furthermore, the emergence of new viral strains and cost of diagnosis contribute to the inability to detect viral agents in order to associate these pathogens with a specific syndrome. However, influenza viruses, one of the major causative agents of acute respiratory tract infections, have been extensively studied with an established global surveillance program. This program was set up to assess the threat of the emergence of strains which could cause pandemic disease [6]. Globally, non-influenza respiratory viruses have received less attention respiratory virus surveillance programs, hence few studies are available in the published literature [7]. Nevertheless, a few previous studies have indicated the risk of non-influenza viruses to public health, and that some viral families have the potential to cause epidemics [8]. The non-influenza respiratory viruses most commonly associated with ARTIs include human respiratory syncytial viruses (HRSV), parainfluenza viruses (HPIVs), and adenoviruses (HAdV), among others [9]. The consequences of these respiratory viruses result in an enormous direct and indirect economic burden on public health. In the United States alone, the estimated annual economic burden of non-influenza viral respiratory tract infections is equivalent to $40 billion [10]. Interestingly, a global incidence of at least 33.1 million has been associated with HRSV in young children under five [11]. The same study indicated a mortality range of 48,000–74,500 for children younger than 5 years and estimated that 99% of these deaths occurred in developing countries [11]. In Sub-Saharan Africa, recent annual incidence data of community-acquired pneumonia is estimated to be 131 million, with significant proportion of these aetiologies due to viruses [12]. A study conducted in Senegal reported that a range of respiratory viruses cause influenza-like illness (ILI) with substantial proportions due to influenza viruses (53.1%; 1045/1967), rhinoviruses (30%; 591/1967), enteroviruses (18.5%; 364/1967), and HRSV (13.5%; 266/1967) in children under five years old [13]. A review of the aetiology of ARTIs in children <5 years in Sub-Saharan Africa showed that HRSVs, HPIVs, and HAdV were among the leading causes of ARTIs [14]. Moreover, in 2018 a systematic review and meta-analysis of HRSV prevalence in Africa reported an overall HRSV prevalence of 14%, thus indicating that this pathogen contributes significantly to severe respiratory illness on the continent [15]. The World Health Organization Regional Office for Africa (WHO-AFRO) 2012 country profiles indicated that acute lower respiratory infections (ALRTIs) were amongst the top three causes of death in the East African Community (EAC). In EAC partner states, the proportionate mortality from lower respiratory tract infections (LRTIs) was: Tanzania (8.7%), Kenya (12.3%), Uganda (9.6%), South Sudan (12%), Rwanda (10%) and Burundi (12.5%). Amongst these EAC states, Kenya, Tanzania, Uganda, and Rwanda have established surveillance programs for influenza and other respiratory viruses which are recognized by the WHO [16]. The	Page 4-6

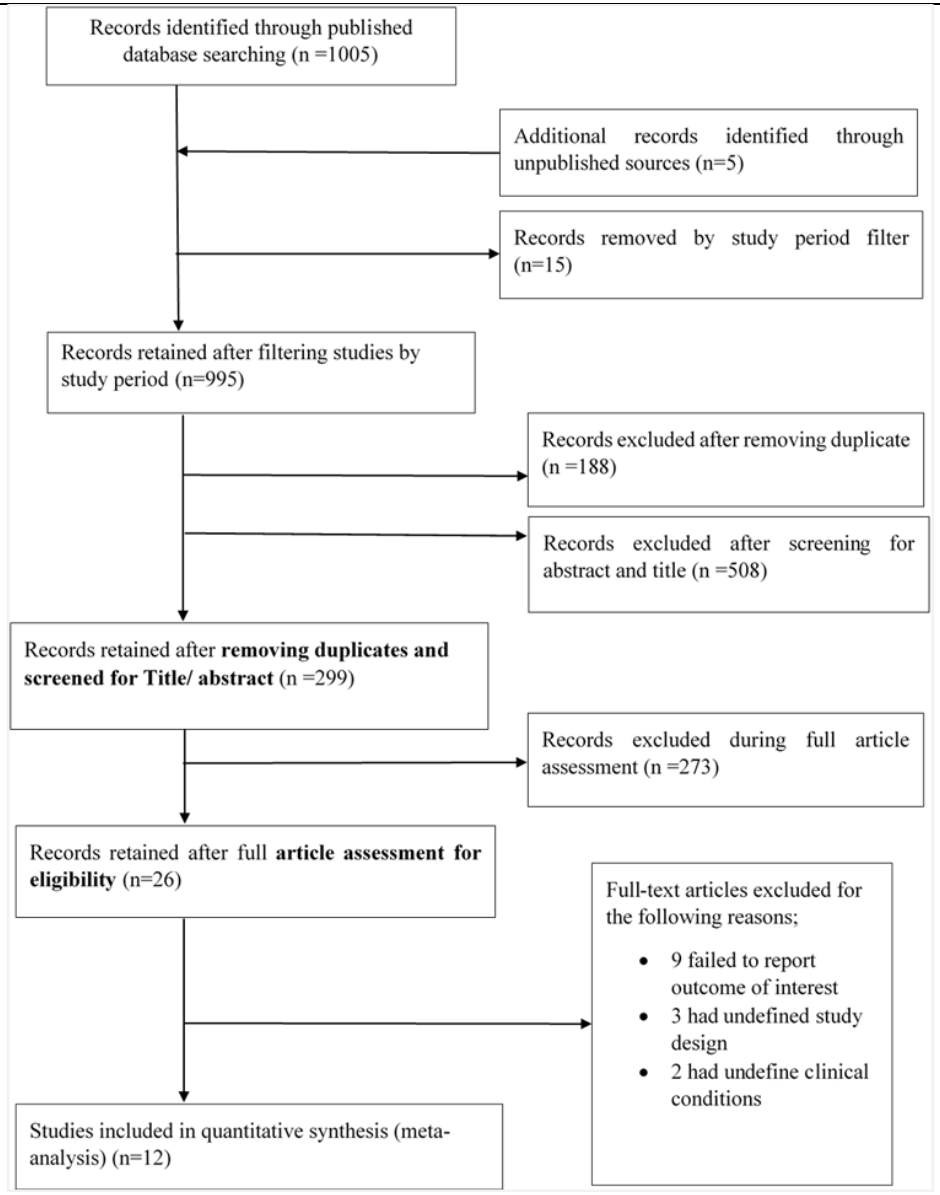
		EAC has a large population with approximately 161 million inhabitants [17] who are highly mobile and integrated, with a common regional market, tourism, and social and cultural exchange. These factors increase the risk of infectious disease transmission and spread in the EAC, as has been described elsewhere [18]. Several other studies have demonstrated various viral aetiologies as causes of ARTIs in the EAC [19,20]. In Kenya, a study conducted at the Kilifi district hospital reported a high prevalence (34%) of HRSV infections in young children which was associated with severe pneumonia [21]. Human parainfluenza, adenoviruses, and other respiratory viruses were also reported [21]. The use of molecular techniques have also enhanced the detection and identification of other non-influenza respiratory viruses in countries with no consistent respiratory disease surveillance programs [22]. A large number of programs for surveillance of influenza-like illness (ILI) and severe acute respiratory illness (SARI) were established in order to strengthen health security after the establishment of the 2005 International Health Regulations. However, such programs have primarily estimated the occurrence of influenza viruses and have either not assessed or not reported other (non-influenza) viruses [23]. This leaves an inconsistent assessment of the epidemiology of non-influenza viruses in the EAC region. This review addresses some of this gap by providing a systematic review of the published and unpublished literature of pooled prevalence of HRSV, HPIV, and HAdV among symptomatic patients in EAC partner states over the period between 2007 and 2020. These three viruses were the most frequent non-influenza respiratory viruses detected in the surveillance programs; the prevalence of other non-influenza viruses was rarely reported, precluding formal systematic review.	
Objectives	4	This review addresses the questions or the gaps of pooled prevalence of HRSV, HPIV, and HAdV among symptomatic patients in EAC partner states over study period from 2007 to 2020 by providing a systematic review of the published and unpublished literature.	Page 6
METHODS			
Protocol and registration	5	PROSPERO: CRD42018110186	Page 10
Eligibility criteria	6	This review considered studies that reported laboratory-confirmed infections caused by HRSV, HPIV, and HAdV in all age groups. These three respiratory viruses are among those frequently reported to cause respiratory tract infections other than influenza. In addition, the review included a broad range of study participants, including those with acute respiratory tract infections (ARTIs), influenza-like illnesses (ILIs), severe acute respiratory illnesses (SARIs), and other syndromes including pneumonia. Studies reporting asymptomatic infections were excluded in this review. The review considered observational studies, including prospective and retrospective cross-sectional and cohort studies that were either descriptive, analytical, or both. Case series, individual case reports, letters to editors, reviews, commentaries, and qualitative studies were excluded. Only studies published in English, including those from unpublished reports from the grey literature, were included. Published studies and	Page 7

		unpublished reports documented in the period between 1st January 2007 and 31st December 2020 were included.	
Information sources	7	An initial unlimited search was conducted in Medline that allowed more refined search strategies tailored for Global Index Medicus. The initial search was performed by verification of the text words contained in the title and abstract of the index terms, which were used to describe the articles using keywords and Medical Subject Heading (MeSH) terminologies (S1). This informed the development of a search strategy that was used for each information source. In addition, reference lists of all studies selected for inclusion were screened for additional relevant publications. The search was first completed in 2019 then updated using the same methodology in 2021. To obtain information from the grey literature, inquiries regarding these viruses were made directly to the ministries of health. We also searched the databases of government medical research institutions, teaching hospitals, and university libraries in EAC partner states. Electronic database search or author correspondence was performed with the Kenya Medical Research Institute (KEMRI) and Kenyatta National Hospital (KNH) for Kenya; National Institute for Medical Research (NIMR) for Tanzania); Uganda Virus Research Institute (UVRI) and Makerere University (MAK), and Mulago Hospital (MUH) for Uganda; Institut National de Sante Public (INSP) for Burundi; and Rwanda Biomedical Center (RBC) for Rwanda. In addition, other non-government public health research programs in the East African Community were contacted. All identified citations were collated and uploaded into Zotero software, version 5.0, (Corporation for Digital Scholarship, Vienna, VA) and duplicates were removed. Titles and abstracts were re-screened against the eligibility criteria, and studies that met the eligibility criteria were retrieved in full and their details imported into JBI SUMARI (Joanna Briggs Institute, Adelaide, Australia). The full texts of selected studies were assessed in detail against the eligibility criteria by two parallel reviewers, and any disagreements were resolved by a third investigator.	Page 7-8
Search	8	Search number Query 21 ((((((prevalence[Title/Abstract]) OR ("Prevalence"[Mesh] OR "epidemiology" [Subheading] OR "Cross-Sectional Studies"[Mesh])) OR incidence[Title/Abstract]) OR ("Incidence"[Mesh] OR "epidemiology" [Subheading] OR "Cohort Studies"[Mesh]))) AND ((((((((((acute viral respiratory infection[Title/Abstract]) OR influenza like illness[Title/Abstract]) OR severe acute respiratory illness[Title/Abstract]) OR respiratory syncytial virus[Title/Abstract]) OR ("Respiratory Syncytial Viruses"[Mesh] OR "Respiratory Syncytial Virus Infections"[Mesh] OR "Respiratory Syncytial Virus, Human"[Mesh])) OR parainfluenza virus[Title/Abstract]) OR ("Parainfluenza Virus 5"[Mesh] OR "Parainfluenza Virus 4, Human"[Mesh] OR "Parainfluenza Virus 3, Human"[Mesh] OR "Parainfluenza Virus 2, Human"[Mesh] OR "Parainfluenza Virus 1, Human"[Mesh])) OR adenovirus[Title/Abstract]) OR ("Adenoviridae Infections"[Mesh] OR "Adenovirus Infections, Human"[Mesh] OR "Adenoviruses, Human"[Mesh])) OR other respiratory virus[Title/Abstract]) OR pneumonia[Title/Abstract]) OR ("Pneumonia"[Mesh] OR "Pneumonia, Viral"[Mesh]))) AND ((east african community[Title/Abstract]) OR ((((((Rwanda[Title/Abstract]) OR Burundi) OR Uganda) OR Kenya) OR Tanzania) OR South Sudan)) Filters: from 2007/1/1 - 2020/12/31	Page 25

		20 Search (east african community[Title/Abstract]) OR ((((((Rwanda[Title/Abstract]) OR Burundi) OR Uganda) OR Kenya) OR Tanzania) OR South Sudan) 19 Search ((((((((((acute viral respiratory infection[Title/Abstract]) OR influenza like illness[Title/Abstract]) OR severe acute respiratory illness[Title/Abstract]) OR respiratory syncytial virus[Title/Abstract]) OR ("Respiratory Syncytial Viruses"[Mesh] OR "Respiratory Syncytial Virus Infections"[Mesh] OR "Respiratory Syncytial Virus, Human"[Mesh])) OR parainfluenza virus[Title/Abstract]) OR ("Parainfluenza Virus 5"[Mesh] OR "Parainfluenza Virus 4, Human"[Mesh] OR "Parainfluenza Virus 3, Human"[Mesh] OR "Parainfluenza Virus 2, Human"[Mesh] OR "Parainfluenza Virus 1, Human"[Mesh])) OR adenovirus[Title/Abstract]) OR ("Adenoviridae Infections"[Mesh] OR "Adenovirus Infections, Human"[Mesh] OR "Adenoviruses, Human"[Mesh])) OR other respiratory virus[Title/Abstract]) OR pneumonia[Title/Abstract]) OR ("Pneumonia"[Mesh] OR "Pneumonia, Viral"[Mesh]) 18 Search (((prevalence[Title/Abstract]) OR ("Prevalence"[Mesh] OR "epidemiology" [Subheading] OR "Cross-Sectional Studies"[Mesh])) OR incidence[Title/Abstract]) OR ("Incidence"[Mesh] OR "epidemiology" [Subheading] OR "Cohort Studies"[Mesh]) 17 Search (((((Rwanda[Title/Abstract]) OR Burundi) OR Uganda) OR Kenya) OR Tanzania) OR South Sudan 16 Search east african community[Title/Abstract] 15 Search "Pneumonia"[Mesh] OR "Pneumonia, Viral"[Mesh] 14 Search pneumonia[Title/Abstract] 13 Search other respiratory virus[Title/Abstract] 12 Search "Adenoviridae Infections"[Mesh] OR "Adenovirus Infections, Human"[Mesh] OR "Adenoviruses, Human"[Mesh] 11 Search adenovirus[Title/Abstract] 10 Search "Parainfluenza Virus 5"[Mesh] OR "Parainfluenza Virus 4, Human"[Mesh] OR "Parainfluenza Virus 3, Human"[Mesh] OR "Parainfluenza Virus 2, Human"[Mesh] OR "Parainfluenza Virus 1, Human"[Mesh] 9 Search parainfluenza virus[Title/Abstract] 8 Search "Respiratory Syncytial Viruses"[Mesh] OR "Respiratory Syncytial Virus Infections"[Mesh] OR "Respiratory Syncytial Virus, Human"[Mesh] 7 Search severe acute respiratory illness[Title/Abstract] 6 Search influenza like illness[Title/Abstract] 5 Search acute viral respiratory infection[Title/Abstract] 4 Search "Incidence"[Mesh] OR "epidemiology" [Subheading] OR "Cohort Studies"[Mesh] 3 Search incidence[Title/Abstract] 2 Search "Prevalence"[Mesh] OR "epidemiology" [Subheading] OR "Cross-Sectional Studies"[Mesh] 1 Search prevalence[Title/Abstract]	

Study selection	9	Before data extraction, all selected studies were critically appraised for methodological quality. This was accomplished with a standardized critical appraisal instrument from the Joanna Briggs Institute by two independent reviewers. This review followed the guideline of systematic reviews of prevalence and incidence manual with the use of JBI SUMARI software available at //www.jbisumari.org.	Page 8
Data collection process	10	All data extracted from selected studies were included in the review using a standardized data extraction tool in JBI SUMARI software by the two independent reviewers.	Page 8
Data items	11	Extracted data consisted of specific details about the names of the primary author, year of publication, locality, age category, clinical condition, study design, length of the study period, specimen type, laboratory test, number of cases, and total population.	Page 8
Risk of bias in individual studies	12	The risk of bias was assessed in the selected studies through the use of an eight variable rating scale [24–27]. Each was given a score for how well-defined and clearly reported the variable was. The variables included: i) length of a study period which was at least three months to permit laboratory processing of samples and analysis, ii) year of documentation or publication, iii) study area (country or study locality), iv) age group description, v) clinical condition or syndrome using a standard case definition, vi) standardized type of specimen collection, vii) laboratory methodology and viii) type of study design. Each variable received a score of one for a clear and defined record and zero for missing or unclear documentation. Thus, the scores could range from 0 to 8. We categorized scores of 0 to 2 as high risk for bias, 3 to 5 as medium risk, and 6 to 8 as low risk.	Page 9
Summary measures	13	Prevalence (proportion)	Page 9
Synthesis of results	14	Data were analysed using Stata®13 (StataCorp, College Station, TX). The dataset was re-organized and coded for analysis, and further meta-analysis was performed using the “metaprop” package in STATA program [28]. Initially, unadjusted prevalence of HRSV, HPIV and HAdV infections were calculated based on the crude numerators and denominators found among the individual studies. To ensure that studies with very small or large prevalence were kept in the overall estimates, the Freeman-Tukey double-arcsine transformation technique was performed using the metaprop command [29]. This procedure stabilized the variance of study-specific prevalence before applying a random-effects model (RE) to assess heterogeneity and generate a pooled prevalence estimate. The random-effects model allowed the effect to vary across studies, providing more conservative estimates with wider confidence intervals given the observed heterogeneity between studies [30]. It was implemented using the method of DerSimonian and Laird [31], whereas 95% confidence intervals (CIs) were drawn from exact binomial distribution (Clopper-Pearson) [32]. The I2 statistic, Cochran’s Q test, and subgroup analysis were used to assess heterogeneity [33]. The statistical values of I2 expressed the variation of in-between studies differences as a percentage, simplifying the interpretation with the “rule of thumb” [33, 34]. Generally, a substantial heterogeneity was indicated by the values of I2 >50%, whereas a tentative categories of minimal (I2<=25%), low (I2=25-4950%), moderate (I2=50-75%), and high (I2>=75%) [33, 35].	Page9-10

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Further assessment, a funnel plot was generated, and an egger test was performed with a metabias command to evaluate the publication bias refer to the “small-study effects” [36]. The Egger test of P<0.10 indicated a significant publication bias [37–39].	Page9-10
Additional analyses	16	Prevalence of infection was described by country, age group, and clinical conditions. In addition, pie-charts were used to display the prevalence of HRSV, HPIV and HAdV infections in the region with quantum geographical information system (qGIS). Subgroup analyses were performed on variables of public health importance including; clinical condition (ILI, SARI, or ARTIs), age groups (below five, five and above, or all ages) and locality (Kenya, Tanzania, or Uganda). We followed guidelines for systematic reviews of prevalence and incidence from the Joanna Briggs Institute to accomplish this review. In addition, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guided the report writing (S2). This review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD42018110186.	Page9-10
RESULTS			
Study selection	17	In this review, we found 1005 records in published databases and 5 reports from unpublished sources. After filtering based on the defined study period (2007-2020), 995 (990 published and 5 unpublished) studies were retained. A total of 299 (294 published and 5 unpublished) were retained after removing 188 duplicates. After screening using the abstract and title, we excluded 508 which did not meet eligibility criteria. The remaining 26 studies were assessed for full article eligibility, and 14 were excluded for different reasons shown in Figure 1. Twelve (12) studies met eligibility criteria and were therefore included in the study with further meta-analysis.	Page10


Records identified through published database searching (n =1005)
Additional records identified through unpublished sources (n=5)
Records removed by study period filter (n=15)
Records retained after filtering studies by study period (n=995)
Records excluded after removing duplicate (n =188)
Records excluded after screening for abstract and title (n =508)
Records retained after **removing duplicates and screened for Title/ abstract** (n =299)
Records excluded during full article assessment (n =273)
Records retained after full **article assessment for eligibility** (n=26)
Full-text articles excluded for the following reasons;
9 failed to report outcome of interest
3 had undefined study design
2 had undefine clinical conditions
Studies included in quantitative synthesis (meta-analysis) (n=12)

Study characteristics	18	In this review, qualified studies were documented from 2009 to 2018 (S3). A large number of studies on the selected viruses were conducted in Kenya (Table 1). These comprised studies of HRSV (n=8, 80%), HPIV (n=6, 75%) and HAdV (n=7, 77.7%) (S4). Tanzania and Uganda had one study each which reported results for all three of the viruses under investigation. There were no available studies from Rwanda, Burundi, and South Sudan that assessed any of the three viruses during the period under review. Most studies reported for the three countries were cross-sectional. Furthermore, the majority of studies (n=6) were of acute respiratory tract infections (ARTIs) involving both ILI and SARI. A few studies (n=4) reported ILI only, and 2 were SARI only. Five studies reported having enrolled individuals of all ages, while four studies recruited participants aged under five years only, and one study exclusively enrolled participants aged five years and older. The majority (n=7) of studies were conducted over a period of >12 months, two were <5 months, and one was 6-12 months. Polymerase chain reaction (PCR) was the most common diagnostic test, and most studies collected and analysed both oropharyngeal swabs (OPS) and nasopharyngeal swabs (NPS) specimens.	Page 11
Risk of bias within studies	19	It was noted that in general, studies had a low risk of bias. Studies reported minimal bias for the HRSV (90%), HPIV (87.5%), and HAdV (88.8%)(Table 1).	Page 11
Results of individual studies	20	The overall pooled prevalence of HRSV was 11% (7-15; 95% CI) reported from 10 studies with a total population of 22,627 participants (S1 Fig). The estimated overall pooled prevalence of 9% (7-11; 95% CI) HPIV was estimated from 8 studies with 28,363 participants (S2 Fig). HAdV overall pooled prevalence was 13% (6-21; 95% CI) recorded in 9 studies with 28,829 participants (S3 Fig)	Page12-13
Synthesis of results	21	A pooled prevalence of 10% (6-15; 95% CI) was found for HRSV, 9% (7-11; 95% CI) for HPIV, and 12% (3-27; 95% CI) for HAdV when restricting the analysis to the studies that investigated ARTIs. Prevalence estimates from ILI studies only found HRSV, HPIV and HAdV prevalences of 5% (95% CI: 4-7, 5% (95% CI: 5-6), and 3% (95% CI: 3-3.5) respectively. In contrast, estimates from SARI studies only were higher for all three viral pathogens at 22% (95% CI: 20-23) for HRSV, 16% (95% CI: 12-21) for HPIV and 18% (95% CI: 16-19) for HAdV. Studies which considered participants of all ages had an estimated prevalence of 9% (95% CI: 5-14), 9% (95% CI: 6-12) and 12% (95% CI: 4-24) for HRSV, HPIV, and HAdV, respectively. Prevalences of 10% (95% CI: 2-24) for HRSV, 6% (95% CI: 4-9) for HPIV, and 15% (95% CI: 13-16) for HAdV were reported in studies that enrolled participants who were under five years of age. In the studies that involved individuals five years and above, HSRV prevalence was similar at 10% (95% CI: 6-15), whereas the prevalence of HPIV and HAdV was much higher at 14% (95% CI: 9-21) and 30% (95% CI: 23-37) respectively. For studies carried out in Kenya, prevalences of HRSV, HPIV and HAdV were 10% (95% CI: 6-15), 9% (95% CI: 7-11) and 14% (95% CI: 7-25) respectively. In Tanzania, estimated prevalence of HAdV and HPIV were similar at 9% (95% CI: 6-12) and 10% (95% CI: 7-14), whereas HRSV prevalence was higher at 29% (95% CI: 24-35). In the studies conducted in Uganda, the corresponding prevalences of HRSV, HPIV, and HAdV were lower at 3% (95% CI: 2-6), 6% (95% CI: 4-9), and 8% (95% CI: 5-12).	Page 13

Risk of bias across studies	22	There was no publication bias suggested by the funnel plot and or the Egger's test (Table 2). Whereas considerable heterogeneity was noted overall and in subgroup analysis, no publication bias was recorded in analysis of subgroups with enough studies to assess (ARTIs, All ages, and Kenya).	Page 14
Additional analysis	23	A similar prevalence to the overall prevalence was documented when restricting the analysis to studies of ARTI: 12% (95% CI: 3-27) for HAdV, 10% (95% CI: 6-15) for HRSV, and 9% (95% CI: 7-11) for HPIV. In addition, studies that involved participants of all ages had a pooled prevalence of 12% (95% CI: 4-24) for HAdV, 9% (95% CI: 5-14) for HRSV, and 9% (95% CI: 6-12) for HPIV. Studies performed in Kenya reported prevalence of 14% (95% CI: 7-25), 10% (95% CI: 6-15), and 9% (95% CI: 7-11) for HAdV, HRSV, and HPIV respectively.	Page 14
DISCUSSION			
Summary of evidence	24	A total of 12 studies were eligible for this meta-analysis. Of these, 10 reported HRSV, 8 HPIV, and 9 HAdV. The overall pooled prevalence of HRSV was 11%, 9% for HPIV, and 13% for HAdV. In general, these respiratory viruses were reported in people with ILI, SARI, and/or ARTIs. Overall, 8 (80%) of the reported studies were done in Kenya.	Page15-16
Limitations	25	This systematic review is subject to several limitations. The systematic searches performed in this review were limited to the most accessible and widely used databases of medical literature, including Medline and Global Index Medicus. In addition, the search was complemented with unpublished literature from major public health institutions and research programs in the EAC. We identified several significant sources of heterogeneity in the estimates of pooled prevalence of HRSV, HPIV, and HAdV, including disease severity, age group, and location. Heterogeneity may also be influenced by other factors, including measured factors such as the length of the study period, study design, and laboratory technique. For example, while most studies used highly sensitive and specific diagnostic PCR tests to detect these virusest, studies which used less sensitive diagnostic methods likely underestimated prevalence. Heterogeneity may also have been influenced by unmeasured factors. Selection of participants may also have been different among the studies, likely resulting in higher prevalence among studies in which patients with more severe illness were enrolled, such as SARI as compared to ILI patients. Additionally, the sample size of studies eligible for inclusion in this analysis was small, limiting the power to detect differences, particularly in subgroup analysis. For example, not all countries of the EAC were represented, and Tanzania and Uganda only had one study each. The small sample size may be due to various factors including limited funding, government policy and priorities, the challenges of information sharing, lack of documentation, inaccessibility of databases, and difficulties with publication of data. Further, the presence of extreme values of prevalence introduced computational complexity which limited our ability to report confidence intervals for the I2 values. Finally, this review only included studies in which patients were selected based on defined medical conditions such as ILI and SARI or ARTIs in general. Studies that included asymptomatic participants were excluded. Asymptomatic patients would likely have had lower prevalences of these viruses than the symptomatic populations used in our study. Therefore the results of this review cannot be generalized to the general population. The exclusion of asymptomatic cases was considered necessary to avoid overdiagnosis of patients who were colonized or carriers of viruses which may not have ever caused disease.	Page17-18

Conclusions	26	Respiratory illness surveillance programs in the EAC have enhanced the detection of both influenza and non-influenza viruses for over a decade. However, there are no platforms for systematic information sharing in the region. It is vital to establish national and regional information-sharing platforms for non-influenza respiratory viruses to guide future research, policy, and development. Our findings indicate that human adenoviruses are the most common sources of ILI and SARI other than influenza infection, followed by the human respiratory syncytial virus and parainfluenza virus. Future studies or research could identify the prevalence of HRSV, HPIV, and HAdV using standardized methods and populations to increase comparability among studies and to account for sources of misclassification and heterogeneity. Additional studies should be considered among older populations, among populations from EAC countries from which no data were found, and asymptomatic populations. In addition, the literature search could include additional databases used in biomedical research. Finally, other emerging respiratory pathogens could be studied and further molecular characterization could be carried out to assess transmission.	Page 19
FUNDING			
Funding	27	NA	Page 20

Annex 11: Fast Fourier transformation data

a) Respiratory Syncytial Virus time-series data and Fast Fourier transformation

Time-OnSet	RSV** positive	IDFT**	Time-OnSet	RSV** positive	IDFT**
Jan-2007	2	1.351424329	**Jan-2009**	8	9.389178108
Feb-2007	4	2.345634546	**Feb-2009**	7	10.85399836
Mar-2007	6	3.260769443	**Mar-2009**	15	11.52811501
Apr-2007	0	3.803398319	**Apr-2009**	7	11.01430817
May-2007	1	3.751316274	**May-2009**	7	9.288823404
Jun-2007	3	3.044333532	**Jun-2009**	15	6.745855897
Jul-2007	2	1.832359858	**Jul-2009**	2	4.112841429
Aug-2007	1	0.459585917	**Aug-2009**	5	2.254224629
Sep-2007	2	-0.616922329	**Sep-2009**	4	1.916392551
Oct-2007	0	-0.954323487	**Oct-2009**	1	3.487280513
Nov-2007	1	-0.260263213	**Nov-2009**	3	6.843902174
Dec-2007	0	1.504155397	**Dec-2009**	12	11.33891708
Jan-2008	1	4.089748915	**Jan-2010**	8	15.93902317
Feb-2008	8	7.008884536	**Feb-2010**	22	19.48415739
Mar-2008	7	9.659824777	**Mar-2010**	30	20.99989044
Apr-2008	13	11.4922694	**Apr-2010**	22	19.97697443
May-2008	16	12.16577777	**May-2010**	15	16.53770489
Jun-2008	13	11.65231151	**Jun-2010**	9	11.43767364
Jul-2008	5	10.24893997	**Jul-2010**	2	5.895937439
Aug-2008	5	8.492918513	**Aug-2010**	3	1.294267977
Sep-2008	13	7.001235774	**Sep-2010**	0	-1.176518562
Oct-2008	4	6.281163521	**Oct-2010**	2	-0.828899031
Nov-2008	14	6.569447193	**Nov-2010**	2	2.334885792
Dec-2008	4	7.751470654	**Dec-2010**	2	7.613511117

Time-OnSet	RSV** positive	IDFT**	Time-OnSet	RSV** positive	IDFT**
Jan-2011	11	13.7780422	**Jan-2013**	2	4.776125944
Feb-2011	17	19.37906383	**Feb-2013**	1	5.839244108
Mar-2011	37	23.10798736	**Mar-2013**	2	6.1445082
Apr-2011	20	24.11720972	**Apr-2013**	9	5.584653432
May-2011	31	22.21610722	**May-2013**	9	4.311798815
Jun-2011	12	17.89460013	**Jun-2013**	0	2.672591658
Jul-2011	5	12.17325408	**Jul-2013**	1	1.08885618
Aug-2011	4	6.325282832	**Aug-2013**	0	-0.075580641
Sep-2011	1	1.548556675	**Sep-2013**	1	-0.619627941
Oct-2011	0	-1.323905991	**Oct-2013**	0	-0.550627646
Nov-2011	2	-2.000687364	**Nov-2013**	0	-0.060923716
Dec-2011	0	-0.755688154	**Dec-2013**	0	0.552301869
Jan-2012	6	1.69784898			
Feb-2012	5	4.439035061			
Mar-2012	5	6.606375725			
Apr-2012	1	7.62441513			
May-2012	7	7.330417858			
Jun-2012	10	5.973577101			
Jul-2012	0	4.097192408			
Aug-2012	3	2.34690762			
Sep-2012	2	1.266309099			
Oct-2012	0	1.140481655			
Nov-2012	12	1.929788375			
Dec-2012	2	3.306579586			

Fast Fourier transform				
	Cycle	**Magnitude**	**Phase**	
	0	569	0	
	1	356.441692	4.473339642	
	2	100.087251	2.437068241	
	3	7.38518152	3.967366378	
	4	81.881598	3.311117909	
	5	71.4078421	1.665583537	
	6	38.3635339	4.067948695	
	7	93.8772921	0.878067626	
	8	152.954032	-0.827990228	
	9	101.67601	3.401667442	
	10	179.784314	0.832998332	
	11	210.918466	-1.211944269	
	12**	180.003756	3.017092179	
	13	86.7767334	1.298906608	
	14	46.5866765	4.700201893	
	15	35.733676	2.833764538	
	16	27.3325614	-0.98953301	
	17	28.6590169	1.439130906	
	18	78.7637152	-0.232446868	
	19	60.4899982	-1.316145551	
	20	39.4032782	2.450047662	
	21	60.3672944	-0.264235728	
	22	71.0818111	3.504223132	
	23	27.3344687	1.895511314	
	24	32.2750708	1.089076509	
****Only 12 component were considered for the analysis**				
****IDFT:Inverse discrete Fourier transform**				
****RSV: Respiratory syncytial virus**				

b) Parainfluenza virus time-series data and Fast Fourier transformation

Time-OnSet	PIV**positive	IDFT**	Time-OnSet	PIV**positive	IDFT**
Jan-2007	0	-0.376540662	**Jan-2009**	9	18.02796
Feb-2007	1	1.236739532	**Feb-2009**	13	18.01838
Mar-2007	0	3.265050835	**Mar-2009**	21	17.42806
Apr-2007	0	5.395291921	**Apr-2009**	24	16.11204
May-2007	7	7.30468551	**May-2009**	16	14.08431
Jun-2007	10	8.742203724	**Jun-2009**	16	11.54792
Jul-2007	15	9.589603553	**Jul-2009**	0	8.873528
Aug-2007	11	9.885295057	**Aug-2009**	4	6.52812
Sep-2007	13	9.804967324	**Sep-2009**	5	4.970108
Oct-2007	7	9.605367768	**Oct-2009**	6	4.537387
Nov-2007	16	9.548183894	**Nov-2009**	5	5.358291
Dec-2007	2	9.826474964	**Dec-2009**	4	7.310212
Jan-2008	4	10.51490359	**Jan-2010**	9	10.03852
Feb-2008	3	11.55748972	**Feb-2010**	21	13.03241
Mar-2008	20	12.79502964	**Mar-2010**	17	15.73928
Apr-2008	23	14.02220583	**Apr-2010**	18	17.68855
May-2008	20	15.05545435	**May-2010**	21	18.59392
Jun-2008	18	15.78960601	**Jun-2010**	19	18.40849
Jul-2008	9	16.22513434	**Jul-2010**	7	17.32028
Aug-2008	13	16.45738413	**Aug-2010**	8	15.69138
Sep-2008	10	16.63149863	**Sep-2010**	14	13.95867
Oct-2008	18	16.87809111	**Oct-2010**	16	12.5233
Nov-2008	34	17.25145112	**Nov-2010**	32	11.65789
Dec-2008	13	17.69202973	**Dec-2010**	6	11.45401

Time-OnSet	PIV**positive	IDFT**	Time-OnSet	PIV**positive	IDFT**
Jan-2011	7	11.82070172	**Jan-2013**	9	14.59499
Feb-2011	12	12.5301672	**Feb-2013**	11	15.67511
Mar-2011	11	13.29437679	**Mar-2013**	8	16.02189
Apr-2011	12	13.84908301	**Apr-2013**	30	15.53523
May-2011	11	14.02147092	**May-2013**	14	14.24513
Jun-2011	15	13.764205	**Jun-2013**	18	12.29908
Jul-2011	18	13.14962645	**Jul-2013**	10	9.927315
Aug-2011	11	12.3299198	**Aug-2013**	4	7.396047
Sep-2011	11	11.4786206	**Sep-2013**	2	4.960386
Oct-2011	16	10.73321093	**Oct-2013**	2	2.826839
Nov-2011	9	10.15673154	**Nov-2013**	0	1.131355
Dec-2011	5	9.729197047	**Dec-2013**	0	-0.06604
Jan-2012	12	9.369548688			
Feb-2012	5	8.979094386			
Mar-2012	12	8.490829936			
Apr-2012	5	7.907575044			
May-2012	11	7.315751807			
Jun-2012	8	6.869515554			
Jul-2012	1	6.749302322			
Aug-2012	7	7.106815351			
Sep-2012	2	8.012687137			
Oct-2012	23	9.422377645			
Nov-2012	23	11.17065119			
Dec-2012	1	12.99688906			

Fast Fourier transform			
Cycle	Magnitude	Phase	
0	940	0	
1	515.2035922	4.404418	
2	105.775605	-1.33489	
3	118.7032828	3.406321	
4	137.666935	3.980966	
5	144.3781839	1.6539	
6	53.00126125	4.685464	
7	87.00554749	-0.48147	
8	149.1333136	3.539104	
9	36.48292675	1.712262	
10	25.68283843	1.10554	
11	83.54733832	4.346245	
12**	59.74542297	3.159648	
13	115.2604462	2.695428	
14	66.62468291	1.064536	
15	19.52693452	1.585509	
16	38.88795761	3.066749	
17	132.0181569	0.972263	
18	73.19374041	-1.08011	
19	63.90708601	0.295341	
20	54.25577106	4.604959	
21	72.01142242	-1.2496	
22	158.25545	2.995526	
23	105.9701564	1.109768	
24	49.17011659	1.125788	
**Only 12 component were considered for the analysis			
**IDFT:Inverse discrete Fourier transform			
**PIV: Parainfluenza virus			

c) Adenovirus time-series data and Fast Fourier transformation

Time-OnSet	AdVs**positive	IDFT**	Time-OnSet	AdVs**positive	IDFT**
Jan-2007	4	2.937735215	**Jan-2009**	5	10.5228183
Feb-07	2	4.536578086	**Feb-2009**	9	10.6643778
Mar-2007	6	6.403739309	**Mar-2009**	15	10.7999421
Apr-2007	10	8.426318081	**Apr-2009**	12	10.9791053
May-2007	15	10.45129891	**May-09**	10	11.2019388
Jun-2007	22	12.2988606	**Jun-2009**	18	11.4167939
Jul-2007	4	13.78427066	**Jul-2009**	5	11.5375398
Aug-2007	6	14.74610745	**Aug-2009**	10	11.474893
Sep-2007	13	15.07604472	**Sep-2009**	13	11.1718136
Oct-2007	19	14.74372336	**Oct-2009**	9	10.6312546
Nov-2007	22	13.81006988	**Nov-2009**	13	9.92645445
Dec-2007	10	12.42415863	**Dec-2009**	12	9.18900441
Jan-2008	7	10.80214703	**Jan-2010**	4	8.57665966
Feb-2008	11	9.191165822	**Feb-2010**	9	8.22930305
Mar-2008	15	7.825155148	**Mar-2010**	7	8.22564855
Apr-2008	2	6.882281824	**Apr-2010**	10	8.55382998
May-2008	2	6.453846288	**May-2010**	7	9.10565351
Jun-2008	4	6.532208486	**Jun-2010**	12	9.69785375
Jul-2008	10	7.020710661	**Jul-2010**	11	10.1159787
Aug-2008	7	7.763004612	**Aug-2010**	9	10.1697701
Sep-2008	13	8.584124783	**Sep-2010**	7	9.745114
Oct-2008	5	9.332545617	**Oct-2010**	13	8.83800927
Nov-2008	22	9.912276662	**Nov-2010**	9	7.56054999
Dec-2008	3	10.29692279	**Dec-2010**	4	6.11643393

Time-OnSet	AdVs**positive	IDFT**	Time-OnSet	AdVs**positive	IDFT**
Jan-2011	2	4.751906623	**Jan-2013**	1	2.80636858
Feb-2011	4	3.694945902	**Feb-2013**	3	2.41451488
Mar-2011	4	3.098900084	**Mar-2013**	1	2.24478583
Apr-2011	3	3.005707282	**Apr-2013**	2	2.27635448
May-2011	5	3.338510717	**May-2013**	3	2.42596163
Jun-2011	2	3.925424775	**Jun-2013**	1	2.57588692
Jul-2011	6	4.547666286	**Jul-2013**	4	2.61071987
Aug-2011	5	4.998652363	**Aug-2013**	5	2.45182242
Sep-2011	9	5.137834933	**Sep-2013**	1	2.07954536
Oct-2011	2	4.924763594	**Oct-2013**	1	1.53729078
Nov-2011	1	4.424612904	**Nov-2013**	0	0.91709659
Dec-2011	1	3.784507539	**Dec-2013**	0	0.3318428
Jan-2012	4	3.188107746			
Feb-2012	8	2.801778879			
Mar-2012	4	2.727645689			
Apr-2012	3	2.976444642			
May-2012	5	3.467113542			
Jun-2012	0	4.052285303			
Jul-2012	1	4.561546253			
Aug-2012	6	4.84955527			
Sep-2012	6	4.835190995			
Oct-2012	4	4.520953348			
Nov-2012	9	3.987889814			
Dec-2012	2	3.36850896			

Fast fourier transform				
	Cycle	**Magnitude**	**Phase**	
	0	591	0	
	1	357.989036	-1.36499	
	2	110.472351	4.564494	
	3	31.9270374	4.521367	
	4	100.691513	-1.15847	
	5	69.4772391	4.418732	
	6	71.0458728	4.408749	
	7	74.3110724	4.039538	
	8	62.1104181	3.25723	
	9	24.5640594	2.674809	
	10	22.4933615	4.148375	
	11	46.1519813	2.56411	
	12**	30.7459011	0.06586	
	13	24.6681751	-0.92536	
	14	39.7437245	4.483586	
	15	29.7539917	-0.88998	
	16	72.1534498	3.977194	
	17	20.4689449	2.936966	
	18	46.1555615	3.112553	
	19	33.0622	1.303646	
	20	20.3609888	4.627995	
	21	24.243393	3.099134	
	22	44.1856576	3.125528	
	23	73.0012755	1.972331	
	24	24.7981032	1.188708	
****Only 12 component were considered for the analysis**				
****IDFT:Inverse discrete Fourier transform**				
****AdV: Adenovirus**				

Annex 12: Twelve eligible studies

No	Title	Author	Year	Country
1	Prevalence of viral aetiologies in children with acute respiratory infections in Nairobi, Kenya	Samwel	2009	Kenya
2	Respiratory Adenovirus Species Circulating In Kenya from 2007-2010	Achilla R et al	2012	Kenya
3	Epidemiology of respiratory viral infections in two long-term refugee camps in Kenya, 2007-2010	Ahmed A.J et al	2012	Kenya
4	Surveillance of Human Parainfluenza viruses in Kenya during the 2007-2011 Period	Mitei K et al	2012	Kenya
5	The viral aetiology of influenza-like illnesses in Kampala and Entebbe, Uganda, 2008	Balinandi S. et al	2013	Uganda
6	Viral and Bacterial Causes of Severe Acute Respiratory Illness Among Children Aged Less Than 5 Years in a High Malaria Prevalence Area of Western Kenya, 2007–2010	Feikin D.R et al	2013	Kenya
7	The burden of influenza and RSV among inpatients and outpatients in rural western Kenya, 2009-2012	Emukule G.O. et al	2014	Kenya
8	Prevalence of respiratory viral pathogens in nasopharyngeal and oropharyngeal specimens and clinical outcomes in young children presenting with severe acute respiratory infections at Kenyatta National Hospital	Gachie L.R. et al	2014	Kenya
9	Etiology and Incidence of Viral Acute Respiratory Infections Among Refugees Aged 5 Years and Older in Hagadera Camp, Dadaab, Kenya	Mohamed Gedi A et al	2015	Kenya
10	The Prevalence of Influenza and other Respiratory Viruses among ILI and SARI patients in Tanzania, from January 2016 to August 2017	Mmbaga V. et al	2018	Tanzania
11	The Burden of Influenza and Respiratory Syncytial Virus in Infants 0-2 Months Old in Rural Western Kenya; Preliminary Data, 2015-2017	Nyawanda O.B et al	2018	Kenya
12	Surveillance of respiratory viruses in the outpatient setting in rural coastal Kenya: baseline epidemiological observations	Nyiro J. U et al	2018	Kenya

Annex 13: Studies bias assessment

No	Author	Study period	Year documentation	Location	Age	Clinical condition	Specimen type	Diagnostic test	Study design	Total score	Bias risk
1	Samwel et al (2009)	1	1	1	1	1	1	1	1	8	low
2	Achilla R et al (2012)	1	1	1	1	1	1	1	1	8	low
3	Ahmed A.J et al (2012)	1	1	1	1	1	1	1	1	8	low
4	Mitei K et al (2012)	1	1	1	0	1	1	1	1	7	low
5	Balinandi S. et al (2013)	1	1	1	1	1	1	1	1	8	low
6	Feikin D.R et al (2013)	1	1	1	1	1	1	1	1	8	low
7	Emukule G.O. et al (2014)	1	1	1	1	1	1	1	1	8	low
8	Gachie L.R. et al (2014)	0	1	1	1	1	1	1	1	7	low
9	Mohamed Gedi A et al (2015)	1	1	1	1	1	1	1	1	8	low
10	Mmbaga V. et al (2018)	0	1	0	0	1	1	1	0	4	moderate
11	Nyawanda O.B et al (2018)	1	1	1	1	1	1	1	1	8	low
12	Nyiro J.U et al (2018)	1	1	1	1	1	1	1	1	8	low
Score category risk of bias											
0-2: High, 3-5: moderate, and 6-8 :low											
Documented and clarity of study characteristic score: 1 (Yes)											
Absence and or unclear of study characteristic score : 0 (No)											

Annex 14: Study participants' clinical characteristics by respiratory viruses

Virus			HRSV			HPIV			HAdVs		
Variable/ Outcome	**Total Pop**	**Proportion**	**Positive**	**Negative**	**Chi-square**	**Positive**	**Negative**	**Chi-square**	**Positive**	**Negative**	**Chi-square**
	N	%	n (%)	n (%)	P-value	n (%)	n (%)	P-value	n (%)	n (%)	P-value
Overall	17261		539(3)	16722(97)		922(5)	16339(95)		581(3)	16680(97)	
Cough		98			0.318			0.683			0.839
Yes	16870		532(3)	16338(97)		905(5)	15965(95)		566(3)	16304(97)	
No	387		7(2)	380(98)		17(4)	370(96)		15(4)	372(96)	
Breathing difficulty					0.921			0.051			0.733
Yes	3954	23	127(3)	3827(97)		181(5)	3773(95)		140(4)	3814(96)	
No	13231		410(3)	12821(97)		737(6)	12494(94)		438(3)	12793(97)	
Chills*		20			<0.001			0.008			0.001
Yes	3424		82(2)	3342(98)		160(5)	3264(95)		80(2)	3344(98)	
No	7870		215(3)	7655(97)		402(5)	7468(95)		278(4)	7592(96)	
Sore throat*		14			0.001			0.019			0.029
Yes	2428		58(2)	2370(98)		101(4)	2327(96)		66(3)	2362(97)	
No	3247		79(98)	3168(98)		176(5)	3071(95)		96(3)	3151(97)	
Muscle Aches		3			0.002			0.36			0.003
Yes	460		4(1)	456(99)		18(4)	442(96)		3(1)	457(99)	
No	3630		95(3)	3535(97)		191(5)	3439(95)		135(4)	3495(96)	
Retro-Orbital pain*		78			0.236			0.508			0.334
Yes	1355		51(4)	1304(96)		71(5)	1284(95)		52(4)	1303(96)	
No	6317		204(3)	6113(97)		354(6)	5963(94)		198(3)	6119(97)	
Malaise*		34			0.013			0.389			0.672
Yes	5954		195(3)	5759(97)		308(5)	5646(95)		193(3)	5761(97)	
No	4006		147(4)	3859(96)		231(6)	3775(94)		143(4)	3863(94)	
Vomiting		32			0.923			0.188			0.735
Yes	5593		174(3)	5419(97)		278(5)	5315(95)		196(4)	5397(96)	
No	11618		364(3)	11254(98)		643(6)	10975(94)		383(3)	11235(97)	

Virus			HRSV			HPIV			HAdVs		
Variable/ Outcome	**Total Pop**	**Proportion**	**Positive**	**Negative**	**Chi-square**	**Positive**	**Negative**	**Chi-square**	**Positive**	**Negative**	**Chi-square**
	N	%	n (%)	n (%)	P-value	n (%)	n (%)	P-value	n (%)	n (%)	P-value
Overall	17261		539(3)	16722(97)		922(5)	16339(95)		581(3)	16680(97)	
Neurological signs*		11			<0.001			0.019			0.031
Yes	1888		23(1)	1865(99)		78(4)	1810(96)		70(4)	1818(96)	
No	12751		438(3)	12313(97)		714(6)	12037(94)		403(3)	12348(97)	
Abdominal Pain*		14			0.005			0.117			0.002
Yes	2452		57(2)	2395(98)		113(5)	2339(95)		61(2)	2391(95)	
No	7526		222(3)	7304(97)		396(5)	7130(95)		239(3)	7287(97)	
Nasal stiffness*		53			0.02			0.642			0.072
Yes	9174		258(3)	8916(97)		477(5)	8697(95)		330(4)	8844(96)	
No	7953		274(3)	7679(97)		437(5)	7516(95)		244(3)	7709(97)	
Runny Nose		87			0.065			0.005			0.056
Yes	15099		488(3)	14611(97)		838(6)	14261(94)		498(3)	14601(97)	
No	2115		49(2)	2066(98)		83(4)	2032(96)		79(4)	2036(96)	
Sputum*		14			<0.001			0.004			0.347
Yes	2508		40(2)	2468(98)		100(4)	2408(96)		76(3)	2432(97)	
No	8577		266(3)	8311(97)		468(5)	8109(95)		305(4)	8272(96)	
Headache*		15			0.129			0.002			<0.001
Yes	2547		67(3)	2480(97)		99(4)	2448(96)		50(2)	2497(98)	
No	2798		79(3)	2719(97)		158(6)	2640(94)		105(4)	2693(96)	
Joint Pain*		5			0.003			0.026			<0.001
Yes	966		15(2)	951(98)		34(4)	932(96)		6(1)	960(99)	
No	3416		93(3)	3323(97)		195(6)	3221(94)		122(4)	3294(94)	
Fatigue		26			0.004			0.058			0.196
Yes	4518		159(4)	4359(96)		242(5)	4276(95)		136(3)	4382(97)	
No	4098		148(4)	3950(96)		247(6)	3851(94)		152(4)	3946(94)	

Virus			HRSV			HPIV			HAdVs		
Variable/ Outcome	**Total Pop**	**Proportion**	**Positive**	**Negative**	**Chi-square**	**Positive**	**Negative**	**Chi-square**	**Positive**	**Negative**	**Chi-square**
	N	%	n (%)	n (%)	P-value	n (%)	n (%)	P-value	n (%)	n (%)	P-value
Overall	17261		539(3)	16722(97)		922(5)	16339(95)		581(3)	16680(97)	
Diarrhea		18			<0.001			0.285			<0.001
Yes	3088		62(2)	3026(98)		153(5)	2935(95)		148(5)	2940(95)	
No	14141		476(3)	13665(97)		766(5)	13375(95)		433(3)	13708(97)	
Bleeding		0.6			0.346			0.718			0.063
Yes	119		2(2)	117(98)		6(5)	113(95)		8(7)	111(93)	
No	17099		537(3)	16562(97)		915(5)	16184(95)		573(3)	16526(97)	
Fever		100			0.035			0.018			0.751
Moderate(37-38.92)	10959		367	10592		621(6)	10338(94)		365(3)	10594(97)	
Severe(39-39.92)	5654		160	5494		278(5)	5376(95)		197(3)	5457(97)	
Very severs(<40)	637		12	625		23(4)	614(96)		19(3)	618(97)	

Annex 15: Clinical characteristics adjusted by age

	HRSV		HPIV		HAdVs	
Variable /Outcome	Adjusted OR* (95%CI)	P-Value	Adjusted OR* (95%CI)	P-Value	Adjusted OR* (95%CI)	P-Value
Age						
≤1year (infant)	Ref		Ref		Ref	
2 to 4 year (Toddler Child)	0.75(0.62-0.91)	0.003	0.90(0.78-1.03)	0.153	0.69(0.58-0.83)	<0.001
5 to ≤ 18year (Child Adolescence)	0.50(0.31-0.79)	0.003	0.45(0.31-0.66)	<0.001	0.29(0.17-0.49)	<0.001
19-49 year (Adult)	0.19(0.04-0.77)	0.02	0.33(0.14-0.76)	0.009	0.08(0.01-0.59)	0.013
50+ year (Sr Adult)	NA					
Chills*						
Yes	Ref		Ref		Ref	
No	1.54(0.75-3.16)	0.229	1.30(0.81-2.09)	0.259	0.82(0.45-1.49)	0.52
Sore throat*						
Yes	Ref		Ref		Ref	
No	0.714(0.40-1.26)	0.25	0.82(0.55-1.24)	0.36	0.65(0.37-1.14)	0.137
Muscle Aches						
Yes	Ref				Ref	
No	2.64(0.30-22.7)	0.376			1.98(0.41-9.50)	0.39
Malaise*						
Yes	Ref					
No	1.00(0.53-1.83)	0.988				
Neurological signs*						
Yes			Ref		Ref	
No			0.44(0.20-0.94)	0.035	1.79(0.23-13.46)	0.57
Abdominal Pain*						
Yes	Ref				Ref	
No	1.33(0.60-2.94)	0.468			0.68(0.39-1.16)	0.161

	HRSV		HPIV		HAdVs	
Variable	**Adjusted OR***	**P-Value**	**Adjusted OR***	**P-Value**	**Adjusted OR***	**P-Value**
/Outcome	**(95%CI)**		**(95%CI)**		**(95%CI)**	
Age						
≤1year (infant)	Ref		Ref		Ref	
2 to 4 year (Toddler Child)	0.75(0.62-0.91)	0.003	0.90(0.78-1.03)	0.153	0.69(0.58-0.83)	<0.001
5 to ≤ 18year (Child Adolescence)	0.50(0.31-0.79)	0.003	0.45(0.31-0.66)	<0.001	0.29(0.17-0.49)	<0.001
19-49 year (Adult)	0.19(0.04-0.77)	0.02	0.33(0.14-0.76)	0.009	0.08(0.01-0.59)	0.013
50+ year (Sr Adult)	NA					
Nasal stiffness*						
Yes	Ref		Ref		Ref	
No	1.61(0.98-2.65)	0.059	0.55(0.26-1.14)	0.112	1.10(0.69-1.75)	0.686
Runny Nose						
Yes					Ref	
No					0.92(0.41-2.09)	0.86
Sputum*						
Yes	Ref		Ref			
No	0.82(0.23-2.88)	0.758	1.41(0.70-2.86)	0.328		
Headache*						
Yes			Ref		Ref	
No			1.23(0.77-1.96)	0.377	0.94(0.56-1.76)	0.866
Joint Pain*						
Yes			Ref		Ref	
No			1.12(0.58-2.16)	0.725	2.23(0.58-8.57)	0.24
Fatigue						
Yes	Ref					
No	1.27(0.60-2.67)					
Diarrhea						
Yes	Ref				Ref	
No	2.64(0.94-7.94)	0.064			0.74(0.42-1.30)	0.299

Annex 16: Ethical approvals

File Copy

KENYA MEDICAL RESEARCH INSTITUTE

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KEMRI/RES/7/3/1 **April 10, 2019**

TO: **UMUHOZA THERESE,**
PRINCIPAL INVESTIGATOR.

THROUGH: **THE DIRECTOR, CVR,**
NAIROBI.

Sponsored Raphael Ulaya 17th April 2019

CENTRE FOR V P.O. Box 5482

Dear Madam,

RE: **KEMRI/SERU/CVR/003/3802** ***(RESUBMISSION OF INITIAL SUBMISSION)*****: A RETROSPECTIVE EVALUATION OF ACUTE VIRAL RESPIRATORY INFECTIONS EPIDEMIOLOGY, CLINICAL CHARACTERISTICS AND RSIKS FACTORS IN KENYA (2007-2012)** ***(VERSION 1.2 DATED FEBRUARY 2019)***

Reference is made to your letter dated February 28, 2019. The KEMRI Scientific and Ethics Review Unit (SERU) acknowledges receipt of the following revised study documents on March 19, 2019;

1. Revised proposal version 1.2 dated February 2019
2. SERU comment letter dated 21 January 2019
3. Copy of ethical approval of the parent protocol dated 05 September 2018
4. Copy of informed consenting of the parent protocol
5. Letter of permission from the Principal Investigator allowing nesting of the sub-study.

This is to inform you that the Committee noted that the issues raised at the 283rd Committee A meeting of the KEMRI Scientific and Ethics Review Unit (SERU) held on **January 15, 2019**, have been adequately addressed.

Consequently, the study is granted approval for implementation effective this day, **April 10, 2019** for a period of **one (1) year**. Please note that authorization to conduct this study will automatically expire on **April 09, 2020.** If you plan to continue with data collection or analysis beyond this date, please submit an application for continuation approval to SERU by **February 26, 2020**.

You are required to submit any proposed changes to this study to SERU for review and the changes should not be initiated until written approval from SERU is received. Please note

that any unanticipated problems resulting from the implementation of this study should be brought to the attention of SERU and you should advise SERU when the study is completed or discontinued.

You may embark on the study.

Yours faithfully,

ENOCK KEBENEI,
THE ACTING HEAD,
KEMRI SCIENTIFIC AND ETHICS REVIEW UNIT.

DEPARTMENT OF THE ARMY
WALTER REED ARMY INSTITUTE OF RESEARCH
503 ROBERT GRANT AVENUE
SILVER SPRING, MD 20910-7500

MCMR-UWZ-C

24 April 2019

MEMORANDUM FOR Umuhoza Thérèse, PhD, Principal Investigator (PI), Department of Emerging Infectious Diseases (DEID) US Army Medical Research Directorate – Africa (USAMRD–A), Unit 8900, Box 330, DPO AE 09831-0330

SUBJECT: Project Qualifies as Not Human Subjects Research, **WRAIR #1267G**

1. A determination was made that the project, **WRAIR #1267G**, entitled, "A Retrospective Investigation of Acute Viral Respiratory Infections Epidemiology, Clinical Characteristics and Risk Factors in Kenya (2007-2012)," (Version 1.2, dated February 2019), qualifies as not human subjects research, and therefore does not require review by the WRAIR Institutional Review Board (IRB) in accordance with WRAIR Policy Letter #12-09, as the PI will not have access to the personal identifiers for the data being obtained from WRAIR# 1267, therefore the activity does not meet the definition of research involving human subjects and 32 CFR 219 does not apply.

2. As a sub-study to the approved protocol, **WRAIR #1267**, this project will acquire and review three datasets of the selected viruses compiled from twelve sentinel sites identified in the parent protocol. The PI and study staff will not have access to Personally Identifiable Information (PII). The objectives of this study are to:

a. Identify the prevalence of infections caused by respiratory syncytial virus (RSV), human para-influenza viruses (HPVIs) and human adenviruses (HAdVs) in Kenya from 2007-2012;

b. Define morbidity burden of infections (such as Influenza-like Illnesses (ILI) and Severe Acute Respiratory Infections (SARI)) caused by RSVs, HPIVs, and HAdvs in sentinel hospital settings of Kenya over the study period;

c. Determine socio-demographic, clinical and climate factors associated with infections caused by RSVs, HPIVs, and HAdvs in Kenya; and

d. Describe a spatiotemporal distribution of infections caused by RSVs, HPIVs and HAdvs in different geographic regions in Kenya over the same period as well as assess seasonality.

3. This project is funded in part by the Global Emerging Infections Surveillance (GEIS) program that supports the parent protocol. Additional funding is provided via the Organization of Women in Science for Developing countries (OWSD).

4. This project was endorsed by COL James Mancuso, MC, former Director, DEID US Army Medical Research Directorate – Kenya (USAMRD–A), as scientifically feasible and valid, militarily relevant, and appropriately resourced on 2 July 2018.

5. The Kenya Medical Research Institute (KEMRI) Scientific Ethics Review Unit (SERU) approved this sub-study on 10 April 2019.

6. In accordance with the U.S. Army Medical Research and Materiel Command (USAMRMC) policy 2018-75, this protocol requires review by the USAMRMC, Office of Research Protections (ORP), Human Research Protections Office (HRPO), as this study involves collaboration with extramural partners. The USAMRMC ORP HRPO approval will need to be obtained and submitted to the Human Subjects Protection Branch (HSPB) prior to the initiation of the study.

7. The WRAIR PI has the responsibility to obtain all business agreements prior to initiation of any work with partners/collaborators or contracted services. This includes any transfer of data or specimens. All relevant business agreements are to remain current throughout the duration of the study and must be maintained by the PI. Failure to obtain business agreements prior to initiation could result in sanctions or disciplinary actions for both the USAMRD–A, Director and the PI. The IRB and Human Subjects Protection Branch (HSPB) will review business agreements as part of monitoring visits to ensure they were obtained as required and report to the WRAIR Commander as to adherence to this requirement. Please seek clarification from the Office of Research Technology and Applications (ORTA).

8. Per the WRAIR Education Policy Letter #11-49, all individuals covered under the WRAIR Human Research Protection Program (HRPP) are required to submit a curriculum vitae (CV) and Collaborative Institutional Training Initiative (CITI) training certificate; documentation of a signed and dated CV, as well as, completed CITI training certificates have been provided for the WRAIR research personnel participating on the protocol. A closeout notification must be submitted to the WRAIR HSPB upon completion of this project.

9. No additional information is required at this time. However, should the objectives change or should WRAIR personnel gain access to identifiers, or the link to personal identifying information, this study would need an additional determination by the Chair, WRAIR IRB or the Director, HSPB, as to whether or not USAMRD-A personnel are engaged in human subjects research, and whether or not WRAIR IRB review and approval are required. No changes, amendments or addenda may be made to the project without prospective approval/acknowledgment. The WRAIR HSPB reserves the right to review the project records and re-assess the research not involving human subjects determination. The WRAIR HSPB also reserves the right to review the project records and re-assess the not human subjects research determination as part of post

approval compliance monitoring. The PI is responsible for maintaining records that confirm that the executed activities match the project that was evaluated and determined to be not human subjects research.

10. The point of contact for this action is the undersigned at (301) 319-9438 or Teresa.r.soderberg.civ@mail.mil.

TERESA R SODERBERG, MA, RAC
Exemption Determination Official
Human Subjects Protection Branch
Walter Reed Army Institute of Research

CF:
Douglas Shaffer, MD
John Distelhorst, MAJ, MC
Professor Wallace Bulimo, PhD
Julius Oyugi, MD
Josephine Kabutu
Michael Obonyo
Jody L. Ference, M.S., CIP, CCRA, CIM
WRAIR ORTA
MCMR-RP

Annex 17: List of peer- reviewed manuscripts

PLOS ONE

RESEARCH ARTICLE

Prevalence and factors influencing the distribution of influenza viruses in Kenya: Seven-year hospital-based surveillance of influenza-like illness (2007–2013)

Therese Umuhoza[1], Wallace D. Bulimo[2,3]*, Julius Oyugi[1], David Schnabel[4], James D. Mancuso[5]

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Check for updates

OPEN ACCESS

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Data Availability Statement: All relevant data are within the manuscript and Supporting Information files.

Funding: The investigators acknowledge funding support from the United States Department of Defense (DoD) Global Emerging Infections Surveillance and Response System (GEIS), which is part of the Armed Forces Health Surveillance Branch (AFHSB) under PROMIS IDs

Abstract

Background

Influenza viruses remain a global threat with the potential to trigger outbreaks and pandemics. Globally, seasonal influenza viruses' mortality range from 291 243–645 832 annually, of which 17% occurs in Sub-Saharan Africa. We sought to estimate the overall prevalence of influenza infections in Kenya, identifying factors influencing the distribution of these infections, and describe trends in occurrence from 2007 to 2013.

Methods

Surveillance was conducted at eight district hospital sites countrywide. Participants who met the case definition for influenza-like illness were enrolled in the surveillance program. The nasopharyngeal specimens were collected from all participants. We tested all specimens for influenza viruses with quantitative reverse transcriptase real-time polymerase chain reaction (RT-qPCR) assay. Bivariate and multivariate log-binomial regression was performed with a statistically significant level of $p<0.005$. An administrative map of Kenya was used to locate the geographical distribution of surveillance sites in counties. We visualized the monthly trend of influenza viruses with a graph and chart using exponential smoothing at a damping factor of 0.5 over the study period (2007–2013).

Results

A total of 17446 participants enrolled in the program. The overall prevalence of influenza viruses was 19% (n = 3230), of which 76% (n = 2449) were type A, 21% (n = 669) type B and 3% (n = 112) A/ B coinfection. Of those with type A, 59% (n = 1451) were not subtyped. Seasonal influenza A/H3N2 was found in 48% (n = 475), influenza A/H1N1/pdm 2009 in 43% (n = 434), and seasonal influenza A/ H1N1 in 9% (n = 88) participants. Both genders

P0136_19_KY_04.01 and P152_20_KY_04.01 for the years 2019 and 2020 respectively.

Competing interests: The authors have declared that no competing interests exist.

were represented, whereas a large proportion of participants 55% were ≤1year age. Influenza prevalence was high, 2 times more in other age categories compared to ≤1year age. Category of occupation other than children and school attendees had a high prevalence of influenza virus (p< <0.001). The monthly trends of influenza viruses' positivity showed no seasonal pattern. Influenza types A and B co-circulated throughout the annual calendar during seven years of the surveillance.

Conclusions

Influenza viruses circulate year-round and occur among children as well as the adult population in Kenya. Occupational and school-based settings showed a higher prevalence of influenza viruses. There were no regular seasonal patterns for influenza viruses.

Introduction

Influenza viruses cause a significant global burden with the potential to trigger devastating outbreaks and or pandemics [1]. Seasonal influenza viruses cause global mortality ranging from 291 243–645 832 individuals annually, 17% of which occurs in Sub-Saharan Africa [2]. To prevent, detect, and respond to the global threat of influenza, the World Health Organization (WHO) established a Global Influenza Surveillance and Response System (GISRS) in 1952 [3, 4]. GISRS monitors the evolution of influenza viruses to provide recommendations for laboratory diagnostics, vaccines formulations, antiviral susceptibility, and risk assessment. The WHO GISRS also serves as a global alert system for the emergence of influenza viruses with pandemic potential. In response to the GISRS network, several nations and partners have progressively initiated an influenza surveillance program to detect influenza virus activities and developed control measures [3].

In the African region, national influenza surveillance programs increased from 21 to 127 for Influenza-like Illness (ILIs) and 2 to 98 for Severe Acute Respiratory Illness (SARI) since 2006 in response to the 2005 international health regulations (IHR) [5]. Before 2006, no comprehensive surveillance of influenza or other viral respiratory illnesses was being undertaken in Kenya. With the emergent pandemic threat due to the then little known virulent avian influenza caused by the highly pathogenic influenza A (H5N1) virus in 2003 [6], the United States Department of Defense's (US DoD) Global Emerging Infections Surveillance and Response System (GEIS) expanded its outreach in respiratory virus surveillance by initiating influenza surveillance to outside continental US (OCONUS) DoD laboratories, including the United States Army Medical Research Unit-Kenya (USAMRU-K) [7]. This was a strategic Force Health Protection response by US DoD to support military readiness by anticipating major health threats to service members in the event of a military operation in this strategic area.

The primary objective of the respiratory surveillance program was to monitor the emergence and characterize the epidemiology and clinical significance of respiratory pathogens with special emphasis on influenza viruses, focusing on civilian and military populations. The specific objective was to identify changes in circulating influenza virus subtypes and genotype strains which may impact disease severity, transmissibility, and treatment and prevention effectiveness across time and geography.

Data from this surveillance program have local and regional benefits. Locally, this endeavor supports the Kenya Ministry of Health (MoH) public health surveillance, one of the most

important functions carried out by the MoH. Through disease surveillance programs, the MoH can prioritize and implement public health interventions in a timely fashion. This program established an influenza surveillance network in Kenya with links between the USAMRU-K, Kenya Defence Forces (KDF), Kenya Medical Research Institute (KEMRI), MoH and WHO. Furthermore, during the period that followed the initiation of surveillance activities, the KEMRI Influenza laboratory gained the required skills and experience through the above partnerships to become a national and regional reference laboratory in 2009. This surveillance system may also provide global benefit through early warning of the circulation of new and dangerous influenza subtypes and local benefits in the event of influenza epidemics. This surveillance system enhanced pandemic preparedness and reporting capabilities required by the 2005 International Health Regulations (IHR) [8]. At the same time, other sentinel influenza systems were also put in place by the MoH with technical support from the Centers for Disease Control and Prevention-Kenya (CDC-K) [9]. These two systems were designed to be complementary, with the DoD system focused on surveillance at district hospitals (sometimes called sub-county hospitals after Kenya government devolution in 2010) and CDC-K surveillance on provincial hospitals (now called county hospitals). The combination of these two systems was expected to give a robust, geographically-representative assessment of the epidemiology of respiratory viruses in Kenya, including the burden of disease, risk factors, trends, and circulating strains.

The influenza surveillance from Kenya's provincial hospitals between 2007 and 2013 has been reported previously [9]. Here, utilizing ILI data collected at district hospitals over roughly the same time period between 2007 and 2013, we complete the picture of influenza virus surveillance in Kenya by estimating the overall prevalence of infection, factors influencing the distribution of infections, and trends of influenza viruses in the country.

Methods

Study sites and population

The joint USAMRU-K and KEMRI protocol for influenza virus surveillance included eight surveillance sites (Fig 1). The study population included all ILI participants for whom the submitted nasopharyngeal specimens met quality control standards in the surveillance program during the period from January 2007 to December 2013 at these sites. Participants included all age groups (infants, children, adults, and elderly) where possible, both gender (male and female) were represented. Surveillance sites were selected accounting for regional population variation, frequency of international movement through the site, and each regional variation in respiratory disease incidence and reporting, and the security situation in the region. The protocol was implemented at several sites including one level five referral hospital (New Nyanza provincial hospital in Kisumu), six district hospitals (Mbagathi district hospital in Nairobi, Malindi district hospital in Kilifi, Port Reitz district hospital in Mombasa, district hospital in Isiolo, district hospital in Kisii, and district hospital in Kericho), and one sub-county hospital (Alupe sub-district hospital in Busia).

A study-specific clinical officer was assigned to each surveillance site. Prior to commencing the study, clinical officers were employed and trained to conduct surveillance for ILI according to the Walter Reed Army Institute of Research (WRAIR) and the KEMRI Institutional Review Boards (IRBs) approved ethical principles under protocol numbers WRAIR#1267 and SSC#981 respectively. Participants with ILI were recruited under the program between January 2007 and December 2013. Participants in the outpatient settings were enrolled if they consented and met the ILI case definition. The informed written consent was obtained from each participant either in English, Kiswahili, or a local language, and the written consent for minors

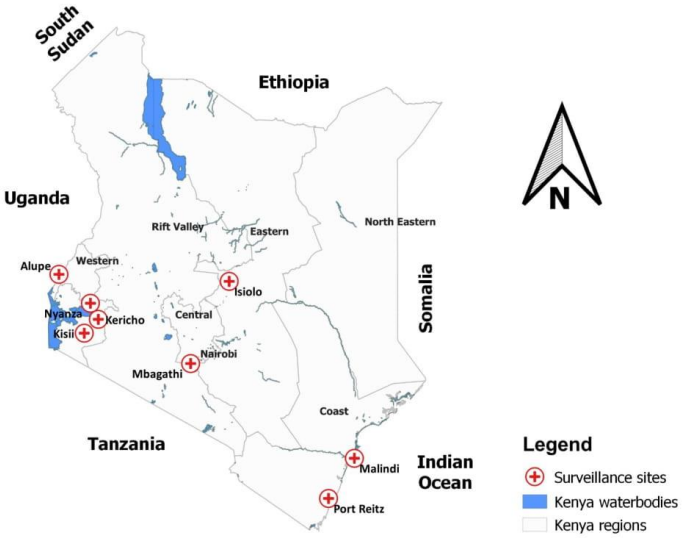

Fig 1. Influenza and other respiratory viruses program surveillance sites.

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was provided by parents or guardians. Participants were recruited during normal working hours specifically on Mondays, Wednesdays, and Fridays. At each surveillance site, a maximum of five participants was eligible for recruitment per day. A questionnaire was administered to all participants to record information including demographics (age, sex, occupation, village, workplace, residence, and travel history), signs & symptoms, and animal exposure.

Case definition

The study adopted the WHO case definition for influenza-like illness (ILI) [10]. This was defined as any individual presenting in outpatient services at the surveillance site with 1) fever >38˚C (oral or equivalent), 2) cough and 3) onset of illness within the previous 10 days.

Specimen processing

The nasopharyngeal specimens were taken using Dacron swabs and placed in 1 ml of Viral Transport Medium (VTM) in a cryovial and immediately stored a dry shipper under liquid nitrogen vapors. In cases where liquid nitrogen was not accessible immediately, the specimens were kept at +4˚C and transported to the laboratory within 48 hours, to be frozen at -80˚C to maintain the cold chain for virus integrity. The cryovials containing the specimens were labeled with unique study numbers using permanent marker pens. The study numbers were assigned by the clinical officer at each surveillance site, who maintained a log of all patients and their study numbers. The study number was the only identifier on the questionnaires and entered in the computerized database established at USAMRU-K. USAMRU-K personnel oversaw the logistics of sample collection, transportation, and accession to the central KEMRI Influenza Laboratory in Nairobi.

Laboratory testing

Detection of influenza viruses in the patient specimens was performed using the quantitative reverse transcriptase real-time polymerase chain reaction (RT-qPCR) assay. The primer and probe sequences for influenza viruses were provided by the CDC. Viral RNA was extracted from patient specimens using the QIAGEN extraction kits following the manufacturer's protocols (QIAGEN GmbH, Hilden, Germany). One-step RT-PCR was performed using the Applied Biosystems 7500Fast instrument (Applied Biosystems Inc; Foster City, CA USA). The initial step for the assay involved a reverse transcription step for 30 minutes at 48˚C followed by transcriptase inactivation for 10 minutes at 95˚C. The thermo-cycling conditions comprised of 45 cycles of denaturation step for 15 seconds at 95˚C, followed by primer annealing at 50˚C and template extension for one minute at 68˚C. All runs were performed together with appropriate controls. The results were interpreted based on cycle threshold (Ct) values in reference to positive and negative controls. Any influenza A and B with Ct value of <40 were considered positive and those with Ct value of ≥ 40 were deemed negative. Samples that tested positive for influenza A were further subtyped for H3N2, H1N1, H5N1, and pandemic H1N1/pdm 2009 using subtype-specific oligonucleotide primers.

Patient data management

All demographic data from the eight surveillance sites were collected using a standard paper questionnaire. Questionnaires and samples were assessed for quality by USAMRU-K laboratory and data managers. The nasopharyngeal samples which met quality control standards were entered into the laboratory management logbooks. Data retrieved from questionnaires were entered into a project-specific Microsoft Access database.

Data analysis

The outcomes of influenza-like illness (ILI) laboratory testing was confirmed for the presence of influenza virus (positive) or absence of influenza virus (negative). The prevalence was expressed as the proportion of positive influenza virus in the total ILI tested population, and the estimate was described by participants' demographic factors and clinical symptoms. The target population included all ILI participants in the surveillance program for the period of 2007 to 2013. We used exact 95% confidence intervals (CI) and chi-square test to measure the differences in demographic variable categories. The log-binomial regression model was performed by bivariate and multivariate to measure the association of predictor variables (demographic and clinical) and the outcome of interest (presence or absence of influenza viruses) with a report of prevalence ratios. We adjusted predictor variables in the multivariate model with a significance level of $p<0.05$ to account for confounding factors. Two-Way interaction was assessed by adding a hashtag symbol (#) in the model where necessary. Finally, the model was selected by the Bayesian Information Criterion (BIC), the lower BIC indicated the best-fitted model. The analysis was performed with STATA®13 (STATA Corporation, College Station, TX, USA). The exponential smoothing with a damping factor of 0.5 was used to visualize the trends over time.

Ethical consideration

Before commencing study activities, the study was reviewed and approved by the Walter Reed Army Institute of Research (WRAIR) Institutional Review Board (IRB) and the Kenya Medical Research Institute (KEMRI) Scientific and Ethics Review Unit (SERU) under protocol numbers WRAIR#1267 and KEMRI/SERU SSC#981 respectively.

Results

Of the eight surveillance sites, 17,446 participants met the enrolment and inclusion criteria. The proportion of participants testing positive for influenza viruses were (19%, N = 3,230), and 81% (N = 14,216) were negative for influenza viruses (Table 1). The demographic characteristics of participants indicated both genders were represented with (52%, N = 9,116) male and (48%, N = 8330) female. A large proportion of participants (55%, N = 9695) were children below one year old (≤1year). The median age in the study population was of 1 year, ranging from 2 months to 75 years. The prevalence of influenza viruses was different in the age categories. Those in the age category of 5 to ≤ 18years had a high prevalence (33%), and as were those in the 19–49 years category (33%). Other age categories including 2–4 years and ≤1year. These two age categories had a proportion of influenza virus (23%) and (13%) respectively. Participants aged ≥ 50 years were represented less, although 21% of these had tested positive for influenza virus. Differences in influenza virus proportions were observed for other demographic factors, including attend school, sick contacts, occupation, and exposure to animals (Table 1). Besides, the influenza proportions varied significantly according to geography and time. There was no substantial difference in the prevalence of influenza viruses for gender categories or residential areas.

Amongst the ILI participants, clinical symptoms varied. Thus, fever (100%), cough (98%), and runny nose (88%) were the most prevalent symptoms (Fig 2). Other clinical characteristics included (53%) nasal stuffiness, (34%) malaise, (32%) vomiting, (26%) fatigue, and (23%) difficulty of breathing. Less than (20%) of participants reported diarrhea, headache, sore throat, sputum, abdominal pain, retro-orbital pain, joint pain, muscle aches, bleeding, and neurological signs.

A crude proportion of clinical symptoms with influenza virus are described in annex table (S1 Table). Since cough and fever were captured in the case definition, we adjusted other clinical symptoms with age categories. The result indicated, only difficult breathing was positively associated with influenza virus prevalence. The prevalence of influenza viruses was less likely in participants without difficulty breathing (PR = 0.68; 95% CI [0.55–0.83], $p<0.0001$) compared to participants with difficulty breathing.

The overall prevalence of influenza viruses during the study period was 19% (n = 3,230). Influenza virus type A was the most common accounting for 76% (n = 2,449), and type B had 21% (n = 669) proportion. Coinfection of subtype A and B were identified in 3% (n = 112) participants. Of those with type A, 59% (n = 1451) were not subtyped and 41% (n = 998) were subtyped. Seasonal A/H3N2 was found in 48% (n = 475), A (H1N1) pdm 2009 in 43% (n = 434), and seasonal A/ H1N1 in 9% (n = 88), and there was one case with a coinfection of strains (A/H3N2) and (A/H1N1) pdm 2009.

For each demographic factor, crude and adjusted prevalence ratios (PRs) of influenza viruses were reported and displayed in Table 2. Both the crude and adjusted models indicated that age categories had a significant association with influenza virus prevalence. The prevalence of influenza was 1.66 times high in 2–4 years old (toddlers) compared to ≤1year (infants). Those of 5 to ≤ 18 years old (children-adolescence) had a higher prevalence of influenza virus 2.2 times more than ≤1year (infants). Influenza virus prevalence was also high 1.9 times in 19–49 years old (adult) compared to ≤1year (infants). Influenza virus prevalence was high 1.2 times in other occupations compared to children category. Those who didn't attend school had a less prevalence of influenza virus, 0.7 lower than school attended participants.

Influenza viruses were found circulating at all surveillance sites (Table 1). The prevalence of influenza showed variability over seven years of the surveillance program. There was year-round influenza viral activity evident in Kenya. We recorded two major spikes in influenza

Table 1. Demographic characteristics of the study participants by influenza virus status.

Variable/	Influenza Positive	Influenza Negative	Total Population	Chi-square*
Outcome	**n (%)**	**n (%)**	**N (%)**	**P-value**
Overall	3230(19%)	14216(81)	17446	
Gender				**0.792**
Male	1681 (18)	7435(82)	9116(52)	
Female	1549(19)	6781(81)	8330(48)	
Age*				**<0.0001**
≤1 year	1296(13)	8399 (87)	9695(55)	
2 to 4 years	1424(23)	4787 (77)	6211(35)	
5 to ≤ 18 years	397(33)	801(67)	1198(6)	
19–49 years	110(33)	218(67)	328 (2)	
50+ years	3 (21)	11(79)	14 (0.08)	
Occupation				**<0.0001**
Children	346(33)	709(67)	1055 (6)	
Other*	2882(18)	13505(82)	16387(94)	
Residence				**0.977**
Urban	3170(19)	13953(81)	17123 (98)	
Rural	60(19)	263 (81)	323 (2)	
Sick contact				**0.016**
Yes	1187(19)	4906(81)	6093(35)	
No	2042(18)	9307(82)	11349(65)	
Attends school				**<0.0001**
Yes	794 (24)	2464(76)	3258(19)	
No	2435 (17)	11745(83)	14180 (81)	
Birds exposure*				**0.022**
Yes	1344(18)	6231(82)	7575(43)	
No	1886(19)	7985(81)	9871(57)	
Pigs exposure				**<0.0001**
Yes	93 (12)	660(88)	753(4)	
No	3137(19)	13556(81)	16693(96)	
Cats exposure				**0.051**
Yes	610(20)	2478(80)	3088(18)	
No	2620(18)	11738(82)	14358(82)	
Location				**<0.0001**
Alupe	140(7)	1741(93)	1881(11)	
Isiolo	259(19)	1085(81)	1344(7)	
Kericho	371(19)	1621(81)	1992(11)	
Kisii	638(22)	2311(78)	2949(17)	
Malindi	249(19)	1077(81)	1326(8)	
Mbagathi	547(19)	2262(81)	2809(16)	
Nyanza	631(21)	2307(79)	2938(17)	
Port Reitz	377(19)	1629(81)	2006(11)	
Year				**<0.0001**
2007	812(28)	2113(72)	2925(17)	
2008	517(17)	2535(83)	3052(17)	
2009	883(23)	2918(77)	3801(22)	
2010	352(12)	2690(88)	3042(17)	
2011	385(17)	1894(83)	2279(13)	

(*Continued*)

Table 1. (Continued)

Variable/	Influenza Positive	Influenza Negative	Total Population	Chi-square*
Outcome	**n (%)**	**n (%)**	**N (%)**	**P-value**
2012	167(12)	1172(88)	1339(8)	
2013	114(11)	894(89)	1008(6)	

Age categories * ≤1 year (infant), 2 to 4 years (Toddler), 5 to ≤ 18 years (Child to Adolescence), 19–49 years (Adult), and 50+ years (Senior Adult). Birds exposure* any domesticated bird. Chi-square* P-value indicates the difference in influenza virus proportion in variable categories. * The category of occupation that included several adult professionals (student, military, other)

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prevalence in May-September, 2007, and September-December 2009 (Fig 3a). Both influenza subtypes A and B co-circulated throughout the year during the seven-year surveillance program. Although some variability existed over the interval, subtype A was generally the most dominant. Seasonal influenza A/H1N1 was seen before the emerging of Influenza A (H1N1) pdm 2009 (Fig 3b). Thereafter, influenza A/seasonal H3N2 was noted to co-circulate with A/2009pandemic H1N1. During the study period, two major influenza outbreaks occurred in Kenya. The first one was due to influenza B in a school in the western region of Kenya in 2006–2007 followed by the 2009–2010 countrywide outbreak, which was part of the pandemic caused by the A/H1N1/pdm09 strain.

Discussion

In this report, among the patients with influenza-like illness (ILI) at the eight surveillance sites in Kenya, 19% were found to have been infected with influenza viruses. The prevalence of influenza infections was slightly higher than the 15% published in the previous study of ILI in provincial hospitals in Kenya [9].

Whereas a greater proportion of influenza virus was noted during the initial years of the surveillance program, i.e. 2007, and in 2009. The proportion of influenza viruses varied over time and location. Those proportions could be attributed to a greater risk of circulating influenza viruses during those initial years, where there were more compliance and enthusiasm in the recruitment than in subsequent years. However, the higher proportion could also be due to

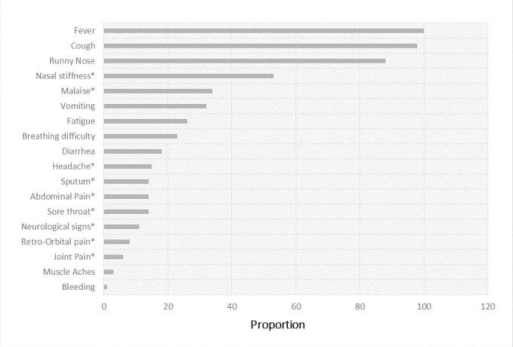

Fig 2. Clinical characteristics of the study participants with influenza-like illness (ILI). *Missing values >10%.

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Table 2. Prevalence ratio of influenza viruses in ILI patients, Kenya (2006–2013).

Variable	Crude PR*	P-Value	Adjusted PR*	P-Value
Outcome	**(95% CI)**		**(95%CI)**	
Gender		0.79		
Male	Ref			
Female	1.00(0.947–1.07)			
Age		**<0.0001**		
≤1 year	Ref		Ref	
2 to 4 years	1.71(1.60–1.83)	<0.0001	1.66(1.55–1.78)	<0.0001
5 to ≤ 18 years	2.47(2.25–2.72)	<0.0001	2.23(2.02–2.46)	<0.0001
19–49 years	2.50(2.13–2.94)	<0.0001	1.93(1.59–2.36)	<0.0001
50+ years	1.60(0.58–4.37)	0.357	1.28(0.47–3.47)	0.628
Occupation		**<0.0001**		
Children	Ref		Ref	
Other	1.86(1.69–2.04)		1.26(1.12–1.41)	<0.0001
Sick contact		**0.016**		
Yes	Ref		Ref	
No	0.92(0.86–0.98)		0.95(0.89–1.02)	0.185
Attends school		**<0.0001**		
Yes	Ref		Ref	
No	0.70(0.65–0.75)		0.76(0.71–0.82)	<0.0001
Birds exposure		**0.022**		
Yes	Ref		Ref	
No	1.07(1.01–1.14)		1.06(0.99–1.13)	0.066
Pigs exposure		**<0.0001**		
Yes	Ref		Ref	
No	1.52(1.25–1.84)		1.36(1.12–1.64)	0.002
Cats exposure		**0.049**		
Yes	Ref		Ref	
No	0.92(0.85–0.99)		0.90(0.83–0.98)	0.023

*PR = Prevalence ratio, CI = Confidence interval Age categories * ≤1 year (infant), 2 to 4 years (Toddler), 5 to ≤ 18 years (Child to Adolescence), 19–49 years (Adult) and 50+ years (Senior Adult). Birds exposure* any domesticated bird. Chi-square* P-value indicates the difference in influenza virus proportion in variable categories. * The category of occupation that included several adult professionals (student, military, other).

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differential recruitment and selection procedures applied during the initial years of the study. As this surveillance system contributed to the early detection and warning of the A/H1N1/pdm 2009 occurrence in Kenya, the proportion for that year is believed to be due to an increased risk of influenza. Influenza A/seasonal H3N2 was generally more prevalent (48%) throughout the study period. Nevertheless, in the early years of the study period when few samples were subtyped, the seasonal A/ H1N1 subtype predominated. The emergence of subtype A/H1N1/pdm 2009 resulted in complete displacement and replacement of seasonal A/H1N1 [11]. This is similar to what was observed in other places in the southern hemisphere during the period of 2009 Influenza pandemic [12]. Similar to other southern hemisphere countries, the seasonal periodicity of influenza virus infections (April-September) was evident in years of greater influenza burden than other years.

The prevalence of influenza virus was high (33%) in the children to adolescence age categories as well as the adult category. Those proportions were similar to the published proportion of influenza-positive (34%) in the older children group in a study conducted among 15 African

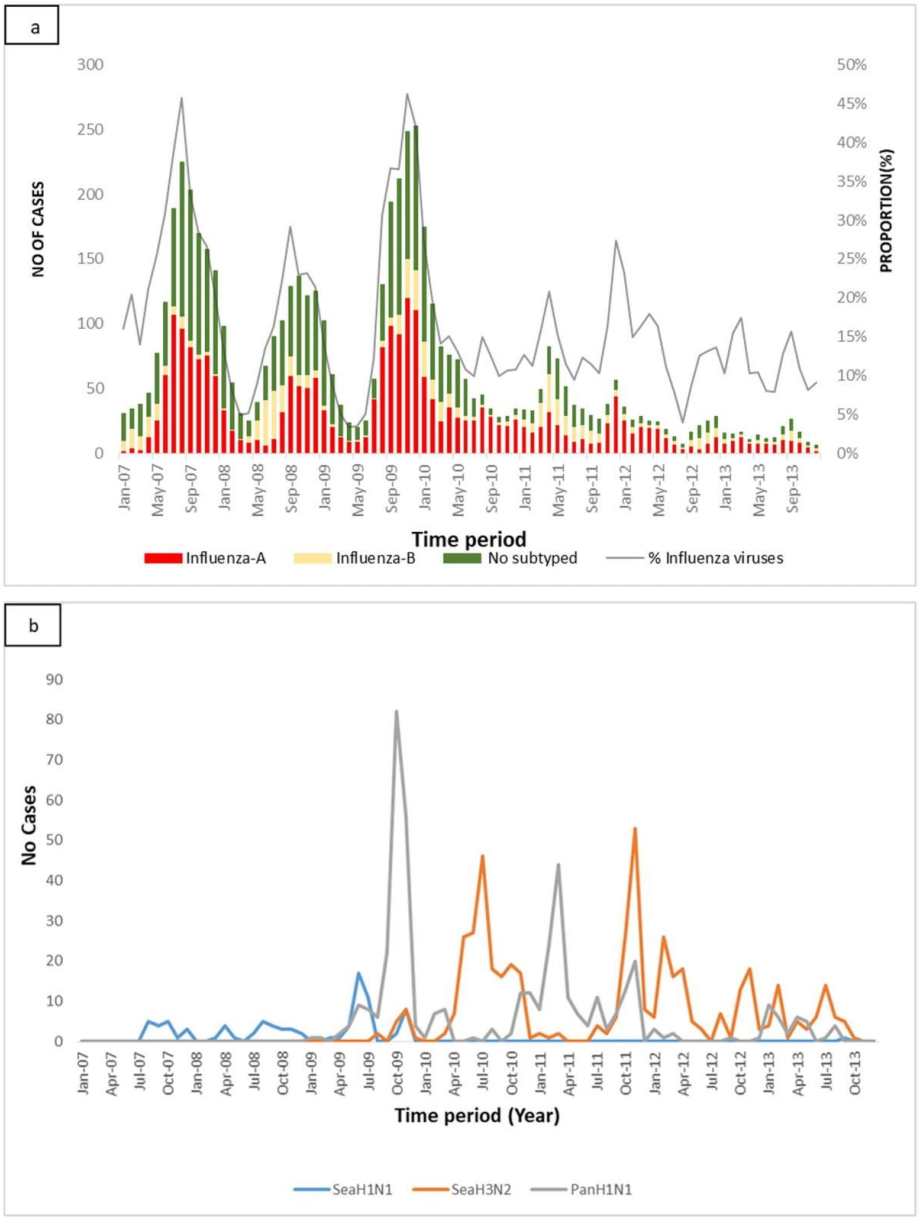

Fig 3. **a**. Influenza viruses monthly trends by Influenza-like Illness (ILI) surveillance program, Kenya. **b**. Influenza virus A subtypes monthly trends by Influenza-like Illness (ILI) surveillance program, Kenya.

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countries [5, 13]. The results differed slightly in other regions of the world including China, India, Colombia, and Peru [14–18]. The difference in prevalence could be explained by the disparities in geography, population diversity, diagnostic methods used, and sampling methods in general. In this study, it was observed that the majority of the study participants were infants (≤1year) and toddlers (2 to 4 years). However, a higher prevalence of the influenza virus occurred in children to adolescence (5 to ≤ 18years) and adults (19–49 years) age categories. It is known that young children including infants and toddlers suffer a heavy burden of ILI, their complications, but this age group is more likely to seek medical care than school or work-aged populations because of the close health attention they receive from the parents/guardians. Therefore, this age group referred to as < 5-year-olds have been over-represented in this study and several previous studies [18–20]. In this study, it was notable that influenza viruses were more prevalent in adult ages. This is not surprising since this age group is recognized to carry more risk factors and other chronic health problems as well as more frequent interactions. This predisposes the adult age population to a range of respiratory infections [21, 22] Thus, due to the predisposing factors, it was possible to capture the adult age population in ILI surveillance programs. Usually, healthy adults with ILI are less likely to seek medical care unless they get severely ill. The school-aged group is at a higher risk of getting infected with influenza viruses [23, 24]. This agreed with our study findings which indicated a high prevalence (24%) of influenza among participants who attended school. In other occupations which included student, military, and other professions, we found a substantial (33%) influenza virus infections. These findings are in agreement with what has been reported elsewhere in militaries, travelers, caregivers, and other people in correctional facilities [25–28].

Many studies have demonstrated interspecies transmission of novel influenza strains in pigs and birds. However, in this study, we were unable to show any interspecies transmission between humans and the various animal species including pigs, birds, and cats. In this report, the prevalence of influenza among those who had household exposure to birds or pigs was similar to or lower than that of those who were not exposed. While this lack of association could be due to factors such as socioeconomic or demographical status, it is more likely that an interspecies transmission is a rare event that is therefore difficult to capture in surveillance studies with a similar study design as ours.

The descriptions of the epidemiology of the influenza viruses in Kenya in this study complement the results of a similar study performed by the CDC during the same period [13]. Our surveillance program was able to not only provide useful data about the routine circulation of influenza viruses but also contributed to responding to influenza outbreaks that occurred in Kenya and the East African region during this period. During the influenza pandemic outbreak in 2009, this surveillance program acted as the *de facto* testing mechanism for Kenya as well as the Republics of Seychelles and Somalia [27]. By leveraging the capacity built-in support of human influenza sentinel surveillance, our program supported the rapid diagnosis and response to the A/H1N1/pdm 2009 influenza pandemic within the region. This is consistent with its objectives and demonstrates the value of these surveillance efforts to public health in Kenya, and globally as well as for both the Kenya Defense Force and the United States military.

Our study may have suffered from several shortfalls. These comprise selection bias in including a high proportion of ILI among children under 5 years old (infants and toddlers), which results in a lower prevalence of infection and limited ability to detect associations in older age groups including senior adult (>50 years). In addition, the study was based on health care facilities at the district level. Due to this higher level of healthcare stratum, it may have included patients who were sicker than the average patient with ILI, resulting in an overestimation of the influenza virus prevalence. Although the sites were selected to provide a thorough representation of the different geography, ecology, and populations of Kenya, there may

be other areas for which these estimates may not be generalizable such as borders, refugee settings, or areas that could not be accessed due to security reasons. Such populations may be at higher risk for both high transmissions of seasonal and emerging influenza strains. Finally, errors in misclassification may have led to an underreporting of the prevalence of influenza infection.

Nevertheless, the strengths of this study are considerable, including the large sample size, broad geographic sampling high-quality sample collection, and processing, well-trained personnel, state-of-the-art equipment and laboratories, and a pre-defined study protocol with comprehensive regulatory support.

Conclusion

Influenza viruses occur commonly among patients with ILI in Kenya and are prevalent in older children and adult populations. Both occupational and school-based settings showed a higher prevalence of influenza viruses. Influenza viruses circulated year-round in Kenya without regular seasonal patterns.

Supporting information

S1 Table. The crude proportion of influenza virus status by clinical characteristics.
(TIF)

Acknowledgments

Disclaimer: Material has been reviewed by the Walter Reed Army Institute of Research (WRAIR). There is no objection to its presentation and/or publication. The opinions or assertions contained herein are the private views of the authors and are not to be construed as official, or as reflecting true views of the Department of the Army or the Department of Defence. The investigators have adhered to the policies for the protection of human subjects as prescribed in AR 70–25.

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Formal analysis: Therese Umuhoza.

Investigation: Therese Umuhoza.

Methodology: Therese Umuhoza.

Project administration: Wallace D. Bulimo.

Resources: Wallace D. Bulimo, James D. Mancuso.

Software: Therese Umuhoza.

Supervision: Wallace D. Bulimo, Julius Oyugi, James D. Mancuso.

Validation: Wallace D. Bulimo, James D. Mancuso.

Visualization: Therese Umuhoza.

Writing – original draft: Therese Umuhoza.

Writing – review & editing: Therese Umuhoza, Wallace D. Bulimo, Julius Oyugi, David Schnabel, James D. Mancuso.

References

1. WHO | Influenza [Internet]. WHO. [cited 2018 Oct 8]. http://www.who.int/influenza/en/
2. Iuliano AD, Roguski KM, Chang HH, Muscatello DJ, Palekar R, Tempia S, et al. Estimates of global seasonal influenza-associated respiratory mortality: a modelling study. The Lancet. 2018 Mar 31; 391 (10127):1285–300.
3. Ziegler T, Mamahit A, Cox NJ. 65 years of influenza surveillance by a World Health Organization-coordinated global network. Influenza Other Respir Viruses. 2018 May 4.
4. Hay AJ, McCauley JW. The WHO global influenza surveillance and response system (GISRS)-A future perspective. Influenza Other Respir Viruses. 2018 May 2.
5. Radin JM, Katz MA, Tempia S, Talla Nzussouo N, Davis R, Duque J, et al. Influenza surveillance in 15 countries in Africa, 2006–2010. J Infect Dis. 2012 Dec 15; 206 Suppl 1:S14–21.
6. Sims LD, Domenech J, Benigno C, Kahn S, Kamata A, Lubroth J, et al. Origin and evolution of highly pathogenic H5N1 avian influenza in Asia. Veterinary Record. 2005 Aug 6; 157(6):159–64. https://doi.org/10.1136/vr.157.6.159 PMID: 16085721
7. Jeremy Sueker J, Blazes DL, Johns MC, Blair PJ, Sjoberg PA, Tjaden JA, et al. Influenza and respiratory disease surveillance: the US military's global laboratory-based network. Influenza Other Respir Viruses. 2010 May 1; 4(3):155–61. https://doi.org/10.1111/j.1750-2659.2010.00129.x PMID: 20409212
8. Sueker JJ, Chretien J-P, Gaydos JC, Russell KL. Global Infectious Disease Surveillance at DoD Overseas Laboratories, 1999–2007. Am J Trop Med Hyg. 2010 Jan; 82(1):23–7. https://doi.org/10.4269/ajtmh.2010.09-0139 PMID: 20064990
9. Katz MA, Muthoka P, Emukule GO, Kalani R, Njuguna H, Waiboci LW, et al. Results from the first six years of national sentinel surveillance for influenza in Kenya, July 2007-June 2013. PLoS ONE. 2014; 9 (6):e98615. https://doi.org/10.1371/journal.pone.0098615 PMID: 24955962
10. Organization WH. WHO recommended surveillance standards. Normes recommandées par l' OMS pour la surveillance [Internet]. 1999 [cited 2019 Dec 3]; https://apps.who.int/iris/handle/10665/65517
11. Gachara G, Majanja J, Njoroge RN, Achilla R, Wurapa EK, Wadegu M, et al. Impact of Influenza A (H1N1)pdm09 Virus on Circulation Dynamics of Seasonal Influenza Strains in Kenya. 2013 Mar [cited 2020 Jul 30]; Available from: https://ir-library.ku.ac.ke/handle/123456789/6725
12. Blyth CC, Kelso A, McPhie KA, Ratnamohan VM, Catton M, Druce JD, et al. The impact of the pandemic influenza A(H1N1) 2009 virus on seasonal influenza A viruses in the southern hemisphere, 2009. Eurosurveillance. 2010 Aug 5; 15(31):19631. PMID: 20738990
13. Maïnassara HB, Lagare A, Tempia S, Sidiki A, Issaka B, Abdou Sidikou B, et al. Influenza Sentinel Surveillance among Patients with Influenza-Like-Illness and Severe Acute Respiratory Illness within the Framework of the National Reference Laboratory, Niger, 2009–2013. PLoS ONE. 2015; 10(7): e0133178. https://doi.org/10.1371/journal.pone.0133178 PMID: 26230666
14. Fu Y, Pan L, Sun Q, Zhu W, Zhu L, Ye C, et al. The Clinical and Etiological Characteristics of Influenza-Like Illness (ILI) in Outpatients in Shanghai, China, 2011 to 2013. PLOS ONE. 2015 Mar 30; 10(3): e0119513. https://doi.org/10.1371/journal.pone.0119513 PMID: 25822885
15. Broor S, Krishnan A, Roy DS, Dhakad S, Kaushik S, Mir MA, et al. Dynamic Patterns of Circulating Seasonal and Pandemic A(H1N1)pdm09 Influenza Viruses From 2007–2010 in and around Delhi, India. PLOS ONE. 2012 Jan 3; 7(1):e29129. https://doi.org/10.1371/journal.pone.0029129 PMID: 22235265
16. Influenza-Like Illness Sentinel Surveillance in Peru. PLOS ONE. 2009 Jul 1; 4(7):e6118. https://doi.org/10.1371/journal.pone.0006118 PMID: 19568433
17. Arango AE, Jaramillo S, Perez J, Ampuero JS, Espinal D, Donado J, et al. Influenza-like illness sentinel surveillance in one hospital in Medellin, Colombia. 2007–2012. Influenza and Other Respiratory Viruses. 2015 Jan 1; 9(1):1–13. https://doi.org/10.1111/irv.12271 PMID: 25100179
18. Emukule GO, Khagayi S, McMorrow ML, Ochola R, Otieno N, Widdowson M-A, et al. The Burden of Influenza and RSV among Inpatients and Outpatients in Rural Western Kenya, 2009–2012. PLOS ONE. 2014 Aug 18; 9(8):e105543. https://doi.org/10.1371/journal.pone.0105543 PMID: 25133576
19. Nair H, Brooks WA, Katz M, Roca A, Berkley JA, Madhi SA, et al. Global burden of respiratory infections due to seasonal influenza in young children: a systematic review and meta-analysis. Lancet. 2011 Dec 3; 378(9807):1917–30. https://doi.org/10.1016/S0140-6736(11)61051-9 PMID: 22078723

20. Cromer D, van Hoek AJ, Jit M, Edmunds WJ, Fleming D, Miller E. The burden of influenza in England by age and clinical risk group: A statistical analysis to inform vaccine policy. Journal of Infection. 2014 Apr 1; 68(4):363–71. https://doi.org/10.1016/j.jinf.2013.11.013 PMID: 24291062

21. Cohen C, Moyes J, Tempia S, Groom M, Walaza S, Pretorius M, et al. Severe Influenza-associated Respiratory Infection in High HIV Prevalence Setting, South Africa, 2009–2011. Emerg Infect Dis. 2013 Nov; 19(11):1766–74. https://doi.org/10.3201/eid1911.130546 PMID: 24209781

22. Ope MO, Katz MA, Aura B, Gikunju S, Njenga MK, Ng'ang'a Z, et al. Risk Factors for Hospitalized Seasonal Influenza in Rural Western Kenya. PLOS ONE. 2011 May 26; 6(5):e20111. https://doi.org/10.1371/journal.pone.0020111 PMID: 21637856

23. Chu Y, Wu Z, Ji J, Sun J, Sun X, Qin G, et al. Effects of school breaks on influenza-like illness incidence in a temperate Chinese region: an ecological study from 2008 to 2015. BMJ Open. 2017 06; 7(3): e013159. https://doi.org/10.1136/bmjopen-2016-013159 PMID: 28264827

24. Nguyen YT, Graitcer SB, Nguyen TH, Tran DN, Pham TD, Le MTQ, et al. National surveillance for influenza and influenza-like illness in Vietnam, 2006–2010. Vaccine. 2013 Sep 13; 31(40):4368–74. https://doi.org/10.1016/j.vaccine.2013.07.018 PMID: 23911781

25. Awofeso N, Fennell M, Waliuzzaman Z, O'Connor C, Pittam D, Boonwaat L, et al. Influenza outbreak in a correctional facility. Aust N Z J Public Health. 2001 Oct; 25(5):443–6. PMID: 11688625

26. Wood S, Telu K, Tribble D, Ganesan A, Kunz A, Fairchok M, et al. Influenza-Like Illness in Travelers to the Developing World. The American Journal of Tropical Medicine and Hygiene. 2018 Nov 7; 99 (5):1269–74. https://doi.org/10.4269/ajtmh.17-0884 PMID: 30226131

27. Cosby MT, Pimentel G, Nevin RL, Fouad Ahmed S, Klena JD, Amir E, et al. Outbreak of H3N2 influenza at a US military base in Djibouti during the H1N1 pandemic of 2009. PLoS ONE. 2013; 8(12):e82089. https://doi.org/10.1371/journal.pone.0082089 PMID: 24339995

28. Turner KB, Levy MH. Prison outbreak: Pandemic (H1N1) 2009 in an Australian prison. Public Health. 2010 Feb 1; 124(2):119–21. https://doi.org/10.1016/j.puhe.2009.12.005 PMID: 20149400

PLOS ONE

RESEARCH ARTICLE

Prevalence of human respiratory syncytial virus, parainfluenza and adenoviruses in East Africa Community partner states of Kenya, Tanzania, and Uganda: A systematic review and meta-analysis (2007–2020)

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Abstract

Background

Viruses are responsible for a large proportion of acute respiratory tract infections (ARTIs). Human influenza, parainfluenza, respiratory-syncytial-virus, and adenoviruses are among the leading cause of ARTIs. Epidemiological evidence of those respiratory viruses is limited in the East Africa Community (EAC) region. This review sought to identify the prevalence of respiratory syncytial virus, parainfluenza, and adenoviruses among cases of ARTI in the EAC from 2007 to 2020.

Methods

A literature search was conducted in Medline, Global Index Medicus, and the grey literature from public health institutions and programs in the EAC. Two independent reviewers performed data extraction. We used a random effects model to pool the prevalence estimate across studies. We assessed heterogeneity with the I^2 statistic, and Cochran's Q test, and further we did subgroup analysis. This review was registered with PROSPERO under registration number CRD42018110186.

Results

A total of 12 studies met the eligibility criteria for the studies documented from 2007 to 2020. The overall pooled prevalence of adenoviruses was 13% (95% confidence interval [CI]: 6–21, N = 28829), respiratory syncytial virus 11% (95% CI: 7–15, N = 22627), and parainfluenza was 9% (95% CI: 7–11, N = 28363). Pooled prevalence of reported ARTIs, all ages,

and locality varied in the included studies. Studies among participants with severe acute respiratory disease had a higher pooled prevalence of all the three viruses. Considerable heterogeneity was noted overall and in subgroup analysis.

Conclusion

Our findings indicate that human adenoviruses, respiratory syncytial virus and parainfluenza virus are prevalent in Kenya, Tanzania, and Uganda. These three respiratory viruses contribute substantially to ARTIs in the EAC, particularly among those with severe disease and those aged five and above.

Introduction

Acute respiratory tract infections (ARTIs) are among the five most common causes of morbidity and mortality globally, accounting for approximately 3.9 million deaths annually. Most of these deaths occur among young children in developing countries [1]. Viruses are responsible for a large proportion of ARTIs and these are associated with various syndromes of the upper and lower respiratory tract, including: acute otitis media, croup, pneumonia, bronchiolitis, and asthma [2, 3]. Additionally, co-infections of viruses and bacteria are commonly reported in severe cases of ARTIs [4, 5]. Although viral aetiologies are associated with a large percentage of acute respiratory tract infections, it is difficult to link specific viral agents to a specific syndrome. This is due to the complexity and broad spectrum of illnesses caused by these pathogens. Furthermore, the emergence of new viral strains and cost of diagnosis contribute to the inability to detect viral agents in order to associate these pathogens with a specific syndrome. However, influenza viruses, one of the major causative agents of acute respiratory tract infections, have been extensively studied with an established global surveillance program. This program was set up to assess the threat of the emergence of strains which could cause pandemic disease [6].

Globally, non-influenza respiratory viruses have received less attention respiratory virus surveillance programs, hence few studies are available in the published literature [7]. Nevertheless, a few previous studies have indicated the risk of non-influenza viruses to public health, and that some viral families have the potential to cause epidemics [8]. The non-influenza respiratory viruses most commonly associated with ARTIs include human respiratory syncytial viruses (HRSV), parainfluenza viruses (HPIVs), and adenoviruses (HAdV), among others [9]. The consequences of these respiratory viruses result in an enormous direct and indirect economic burden on public health. In the United States alone, the estimated annual economic burden of non-influenza viral respiratory tract infections is equivalent to $40 billion [10]. Interestingly, a global incidence of at least 33.1 million has been associated with HRSV in young children under five [11]. The same study indicated a mortality range of 48,000–74,500 for children younger than 5 years and estimated that 99% of these deaths occurred in developing countries [11].

In Sub-Saharan Africa, recent annual incidence data of community-acquired pneumonia is estimated to be 131 million, with significant proportion of these aetiologies due to viruses [12]. A study conducted in Senegal reported that a range of respiratory viruses cause influenza-like illness (ILI) with substantial proportions due to influenza viruses (53.1%; 1045/1967), rhinoviruses (30%; 591/1967), enteroviruses (18.5%; 364/1967), and HRSV (13.5%; 266/1967) in children under five years old [13]. A review of the aetiology of ARTIs in children <5 years in

Sub-Saharan Africa showed that HRSVs, HPIVs, and HAdV were among the leading causes of ARTIs [14]. Moreover, in 2018 a systematic review and meta-analysis of HRSV prevalence in Africa reported an overall HRSV prevalence of 14%, thus indicating that this pathogen contributes significantly to severe respiratory illness on the continent [15].

The World Health Organization Regional Office for Africa (WHO-AFRO) 2012 country profiles indicated that acute lower respiratory infections (ALRTIs) were amongst the top three causes of death in the East African Community (EAC). In EAC partner states, the proportionate mortality from lower respiratory tract infections (LRTIs) was: Tanzania (8.7%), Kenya (12.3%), Uganda (9.6%), South Sudan (12%), Rwanda (10%) and Burundi (12.5%). Amongst these EAC states, Kenya, Tanzania, Uganda, and Rwanda have established surveillance programs for influenza and other respiratory viruses which are recognized by the WHO [16]. The EAC has a large population with approximately 161 million inhabitants [17] who are highly mobile and integrated, with a common regional market, tourism, and social and cultural exchange. These factors increase the risk of infectious disease transmission and spread in the EAC, as has been described elsewhere [18]. Several other studies have demonstrated various viral aetiologies as causes of ARTIs in the EAC [19, 20]. In Kenya, a study conducted at the Kilifi district hospital reported a high prevalence (34%) of HRSV infections in young children which was associated with severe pneumonia [21]. Human parainfluenza, adenoviruses, and other respiratory viruses were also reported [21]. The use of molecular techniques have also enhanced the detection and identification of other non-influenza respiratory viruses in countries with no consistent respiratory disease surveillance programs [22].

A large number of programs for surveillance of influenza-like illness (ILI) and severe acute respiratory illness (SARI) were established in order to strengthen health security after the establishment of the 2005 International Health Regulations. However, such programs have primarily estimated the occurrence of influenza viruses and have either not assessed or not reported other (non-influenza) viruses [23]. This leaves an inconsistent assessment of the epidemiology of non-influenza viruses in the EAC region. This review addresses some of this gap by providing a systematic review of the published and unpublished literature of pooled prevalence of HRSV, HPIV, and HAdV among symptomatic patients in EAC partner states over the period between 2007 and 2020. These three viruses were the most frequent non-influenza respiratory viruses detected in the surveillance programs; the prevalence of other non-influenza viruses was rarely reported, precluding formal systematic review.

Methods

Eligibility criteria

This review considered studies that reported laboratory-confirmed infections caused by HRSV, HPIV, and HAdV in all age groups. These three respiratory viruses are among those frequently reported to cause respiratory tract infections other than influenza. In addition, the review included a broad range of study participants, including those with acute respiratory tract infections (ARTIs), influenza-like illnesses (ILIs), severe acute respiratory illnesses (SARIs), and other syndromes including pneumonia. Studies reporting asymptomatic infections were excluded in this review.

The review considered observational studies, including prospective and retrospective cross-sectional and cohort studies that were either descriptive, analytical, or both. Case series, individual case reports, letters to editors, reviews, commentaries, and qualitative studies were excluded. Only studies published in English, including those from unpublished reports from the grey literature, were included. Published studies and unpublished reports documented in the period between 1st January 2007 and 31st December 2020 were included.

Search strategy

An initial unlimited search was conducted in Medline that allowed more refined search strategies tailored for Global Index Medicus. The initial search was performed by verification of the text words contained in the title and abstract of the index terms, which were used to describe the articles using keywords and Medical Subject Heading (MeSH) terminologies (S1 File). This informed the development of a search strategy that was used for each information source. In addition, reference lists of all studies selected for inclusion were screened for additional relevant publications. The search was first completed in 2019 then updated using the same methodology in 2021.

To obtain information from the grey literature, inquiries regarding these viruses were made directly to the ministries of health. We also searched the databases of government medical research institutions, teaching hospitals, and university libraries in EAC partner states. Electronic database search or author correspondence was performed with the Kenya Medical Research Institute (KEMRI) and Kenyatta National Hospital (KNH) for Kenya; National Institute for Medical Research (NIMR) for Tanzania; Uganda Virus Research Institute (UVRI) and Makerere University (MAK), and Mulago Hospital (MUH) for Uganda; Institut National de Sante Public (INSP) for Burundi; and Rwanda Biomedical Center (RBC) for Rwanda. In addition, other non-government public health research programs in the East African Community were contacted.

All identified citations were collated and uploaded into Zotero software, version 5.0, (Corporation for Digital Scholarship, Vienna, VA) and duplicates were removed. Titles and abstracts were re-screened against the eligibility criteria, and studies that met the eligibility criteria were retrieved in full and their details imported into JBI SUMARI (Joanna Briggs Institute, Adelaide, Australia). The full texts of selected studies were assessed in detail against the eligibility criteria by two parallel reviewers, and any disagreements were resolved by a third investigator.

Data extraction and management

Prior to data extraction, all selected studies were critically appraised for methodological quality. This was accomplished with a standardized critical appraisal instrument from the Joanna Briggs Institute by two independent reviewers. This review followed the guideline of systematic reviews of prevalence and incidence manual with the use of JBI SUMARI software available at //www.jbisumari.org.

All data extracted from the selected studies were included in the review using a standardized data extraction tool in JBI SUMARI software. Extracted data consisted of: name of the primary author, year of publication, locality, age categories of participants, clinical characteristics, study design, length of the study period, specimen type, laboratory test type, number of cases, and total population. Age categories were reported as under five years only, five and above only, or all ages. Clinical conditions or syndromes were recorded as influenza-like illness (ILI) only, severe acute respiratory illness (SARI) only, or acute respiratory tract infections (ARTIs) for studies which investigated both ILI and SARI. Pneumonia was categorized as a severe acute respiratory illness (SARI). Study durations were classified as five months or less, six to twelve months, and more than twelve months.

Risk of bias assessment

The risk of bias was assessed in the selected studies through the use of an eight variable rating scale [24–27]. Each was given a score for how well-defined and clearly reported the variable was. The variables included: i) length of a study period which was at least three months to

permit laboratory processing of samples and analysis, ii) year of documentation or publication, iii) study area (country or study locality), iv) age group description, v) clinical condition or syndrome using a standard case definition, vi) standardized type of specimen collection, vii) laboratory methodology and viii) type of study design. Each variable received a score of one for a clear and defined record and zero for missing or unclear documentation. Thus, the scores could range from 0 to 8. We categorized scores of 0 to 2 as high risk for bias, 3 to 5 as medium risk, and 6 to 8 as low risk.

Data synthesis and analysis

Data were analysed using Stata® 13 (StataCorp, College Station, TX). The dataset was re-organized and coded for analysis, and further meta-analysis was performed using the "metaprop" package in STATA program [28]. Initially, unadjusted prevalence of HRSV, HPIV and HAdV infections were calculated based on the crude numerators and denominators found among the individual studies.

To ensure that studies with very small or large prevalence were kept in the overall estimates, the Freeman-Tukey double-arcsine transformation technique was performed using the metaprop command [29]. This procedure stabilized the variance of study-specific prevalence before applying a random-effects model (RE) to assess heterogeneity and generate a pooled prevalence estimate. The random-effects model allowed the effect to vary across studies, providing more conservative estimates with wider confidence intervals given the observed heterogeneity between studies [30]. It was implemented using the method of DerSimonian and Laird [31], whereas 95% confidence intervals (CIs) were drawn from exact binomial distribution (Clopper-Pearson) [32]. The I^2 statistic, Cochran's Q test, and subgroup analysis were used to assess heterogeneity [33]. The statistical values of I^2 expressed the variation of in-between studies differences as a percentage, simplifying the interpretation with the "rule of thumb" [33, 34]. Generally, a substantial heterogeneity was indicated by the values of I^2 >50%, whereas a tentative categories of minimal (I^2< = 25%), low (I^2 = 25–4950%), moderate (I^2 = 50–75%), and high (I^2> = 75%)[33, 35]. A funnel plot was generated and an egger test was performed with a metabias command to evaluate for publication bias [36]. The Egger test of P<0.10 indicated a significant publication bias [37–39].

Prevalence of infection was described by country, age group, and clinical conditions. In addition, pie charts were used to display the prevalence of HRSV, HPIV and HAdV infections in the region with quantum geographical information system (qGIS). Subgroup analyses were performed on variables of public health importance including: clinical condition (ILI, SARI, or ARTIs), age groups (below five, five and above, or all ages), and locality (Kenya, Tanzania, or Uganda). We followed guidelines for systematic reviews of prevalence and incidence from the Joanna Briggs Institute to accomplish this review. In addition, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guided the report writing (S2 File). This review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD42018110186.

Results

Review records

In this review, we found 1005 records in published databases and 5 reports from unpublished sources. After filtering based on the defined study period (2007–2020), 995 (990 published and 5 unpublished) studies were retained. A total of 299 (294 published and 5 unpublished) were retained after removing 188 duplicates. After screening using the abstract and title, we excluded 508 which did not meet eligibility criteria. The remaining 26 studies were assessed

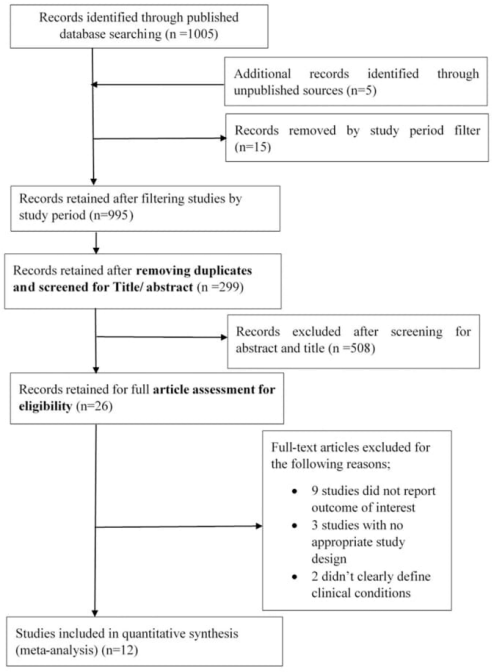

Fig 1. Review records.

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for full article eligibility, and 14 were excluded for different reasons shown (Fig 1). Twelve (12) studies met eligibility criteria and were therefore included in the study with further meta-analysis.

Characteristics of selected studies

In this review, qualified studies were documented from 2009 to 2018 (S3 File). A large number of studies on the selected viruses were conducted in Kenya (Table 1). These comprised studies of HRSV (n = 8, 80%), HPIV (n = 6, 75%) and HAdV (n = 7, 77.7%) (S4 File). Tanzania and Uganda had one study each which reported results for all three of the viruses under investigation. There were no available studies from Rwanda, Burundi, and South Sudan that assessed any of the three viruses during the period under review. Most studies reported for the three countries were cross-sectional. Furthermore, the majority of studies (n = 6) were of acute respiratory tract infections (ARTIs) involving both ILI and SARI. A few studies (n = 4) reported ILI only, and 2 were SARI only. Five studies reported having enrolled individuals of all ages, while four studies recruited participants aged under five years only, and one study exclusively enrolled participants aged five years and older. The majority (n = 7) of studies were conducted over a period of >12 months, two were <5 months, and one was 6–12 months. Polymerase chain reaction (PCR) was the most common diagnostic test, and most studies collected and analysed both oropharyngeal swabs (OPS) and nasopharyngeal swabs (NPS) specimens. In general, the studies had a low risk of bias.

Table 1. Study characteristics.

Outcomes	HRSV		HPIV		HAdV	
Study	**Number (n)**	**Proportion (%)**	**Number (n)**	**Proportion (%)**	**Number (n)**	**Proportion (%)**
Locality						
Kenya	8	80	6	75	7	77.7
Tanzania	1	10	1	12.5	1	11.1
Uganda	1	10	1	12.5	1	11.1
Clinical Condition						
ILI	2	20	2	25	2	22.2
SARI	2	20	1	62.5	2	22.2
ARTIs*	6	60	5	12.5	5	55.5
Population						
Under Five	3	30	1	12.5	2	22.2
Five and above	1	10	1	12.5	1	11.1
All ages**	5	50	4	50	5	55.5
Study design						
Cross-sectional	7	70	6	75	7	77.7
Cohort	2	20	1	12.5	1	11.1
Study Period						
Short-term (≤ months)	2	20	2	25	2	22.2
Medium-term (6–12 months)	1	10	1	12.5	1	11.1
Long-term (>12 months)	5	50	3	37.5	4	44.4
Lab Test						
Virus isolation	1	10	2	25	2	22.2
PCR	9	90	6	75	7	77.7
Specimens						
OPS	1	10	1	12.5	1	11.1
NPS	2	20	3	37.5	3	33.3
OPS and NPS	7	70	4	50	5	55.5
Risk of Bias						
Low risk	9	90	7	87.5	8	88.8
Moderate risk	1	10	1	12.5	1	11.1

*ARTIs studies of both ILI and SARI.

**All ages included uncategorized age groups.

OPS = oropharyngeal swabs, NPS = nasopharyngeal swabs, PCR = polymerase chain reaction, ARTI = acute respiratory tract infection, ILI = influenza-like illness, SARI = severe acute respiratory illness, HRSV = human respiratory syncytial virus, HPIV = human parainfluenza virus, and HAdV = human adenovirus.

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Prevalence of human respiratory syncytial virus, parainfluenza and adenoviruses

The overall pooled prevalence of HRSV was 11% (95% CI: 7–15) reported from 10 studies with a total population of 22,627 participants (Fig 2).

The estimated overall pooled prevalence of 9% (95% CI: 7–11) HPIV was estimated from 8 studies with 28,363 participants (Fig 3).

HAdV overall pooled prevalence was 13% (95% CI: 6–21) recorded in 9 studies with 28,829 participants (Fig 4).

Substantial heterogeneity in the pooled prevalence of the three viruses was seen in the included studies, according to severity of illness, age group, and locality. Prevalence of the three viruses differed in the three countries (Fig 5).

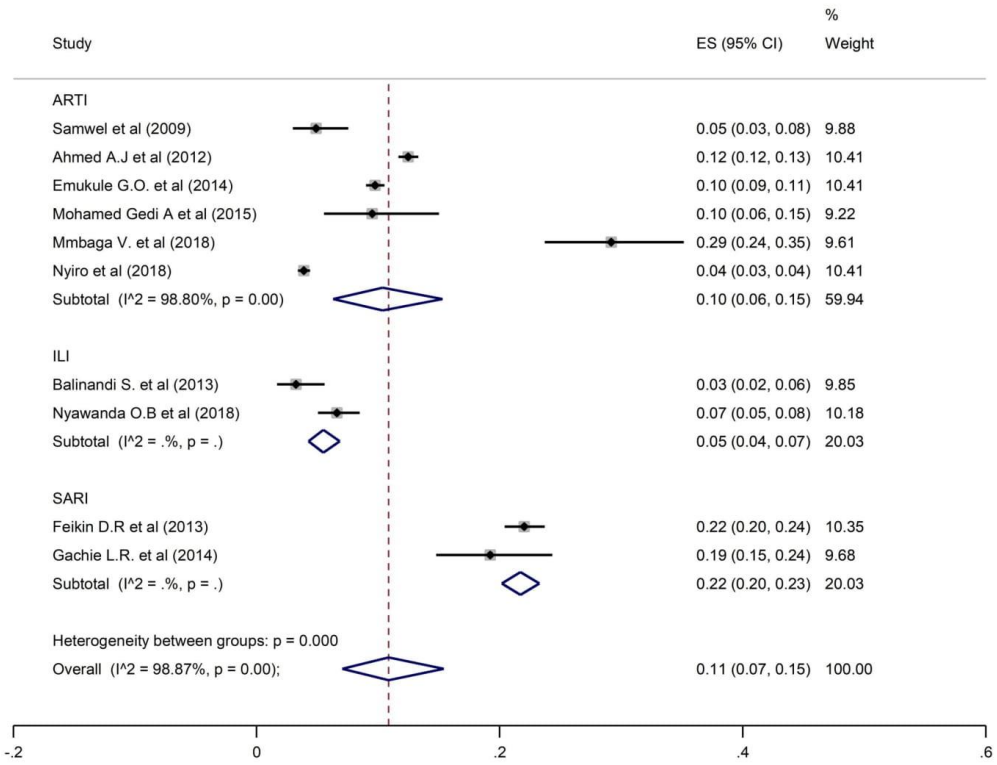

Fig 2. Pooled prevalence of HRSV in ARTIs, ILI, and SARI.

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A pooled prevalence of 10% (6–15; 95% CI) was found for HRSV, 9% (7–11; 95% CI) for HPIV, and 12% (3–27; 95% CI) for HAdV when restricting the analysis to the studies that investigated ARTIs. Prevalence estimates from ILI studies only found HRSV, HPIV and HAdV prevalences of 5% (95% CI: 4–7, 5% (95% CI: 5–6), and 3% (95% CI: 3–3.5) respectively. In contrast, estimates from SARI studies only were higher for all three viral pathogens at 22% (95% CI: 20–23) for HRSV, 16% (95% CI: 12–21) for HPIV and 18% (95% CI: 16–19) for HAdV.

Studies which considered participants of all ages had an estimated prevalence of 9% (95% CI: 5–14), 9% (95% CI: 6–12) and 12% (95% CI: 4–24) for HRSV, HPIV, and HAdV, respectively. Prevalences of 10% (95% CI: 2–24) for HRSV, 6% (95% CI: 4–9) for HPIV, and 15% (95% CI: 13–16) for HAdV were reported in studies that enrolled participants who were under five years of age. In the studies that involved individuals five years and above, HSRV prevalence was similar at 10% (95% CI: 6–15), whereas the prevalence of HPIV and HAdV was much higher at 14% (95% CI: 9–21) and 30% (95% CI: 23–37) respectively.

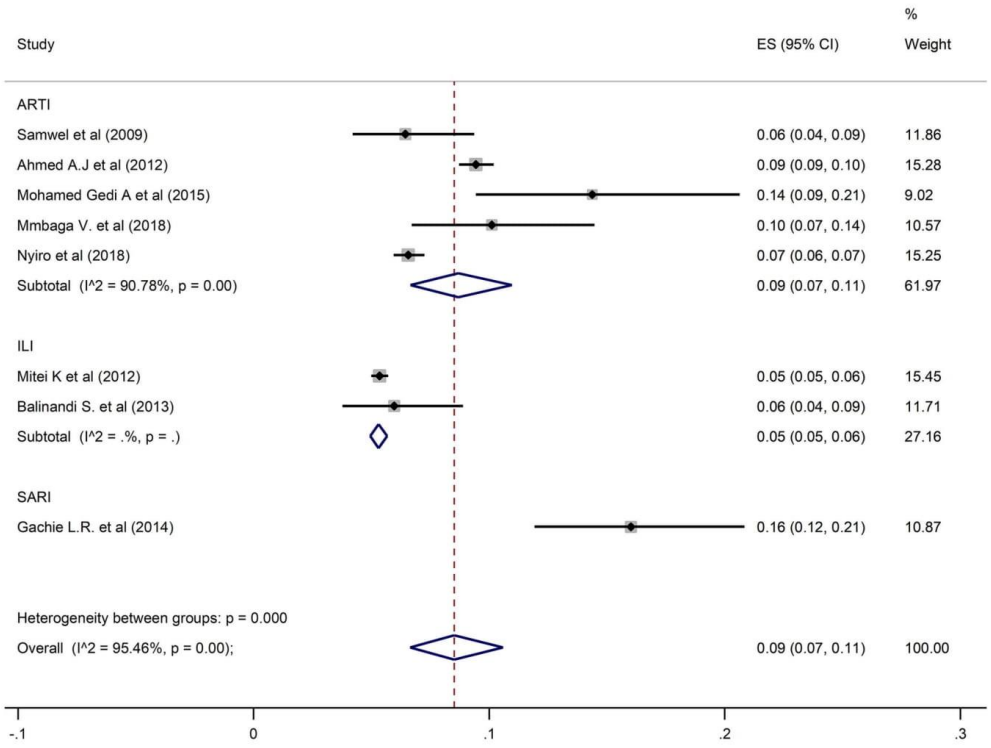

Fig 3. Pooled prevalence of HPIV in ARTIs, ILI, and SARI.

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For studies carried out in Kenya, prevalences of HRSV, HPIV and HAdV were 10% (95% CI: 6–15), 9% (95% CI: 7–11) and 14% (95% CI: 7–25) respectively. In Tanzania, estimated prevalence of HAdV and HPIV were similar at 9% (95% CI: 6–12) and 10% (95% CI: 7–14), whereas HRSV prevalence was higher at 29% (95% CI: 24–35). In the studies conducted in Uganda, the corresponding prevalences of HRSV, HPIV, and HAdV were lower at 3% (95% CI: 2–6), 6% (95% CI: 4–9), and 8% (95% CI: 5–12).

There was no publication bias suggested by the funnel plot and or the Egger's test (Table 2). Whereas considerable heterogeneity was noted overall and in subgroup analysis, no publication bias was recorded in analysis of subgroups with enough studies to assess (ARTIs, All ages, and Kenya). A similar prevalence to the overall prevalence was documented when restricting the analysis to studies of ARTI: 12% (95% CI: 3–27) for HAdV, 10% (95% CI: 6–15) for HRSV, and 9% (95% CI: 7–11) for HPIV. In addition, studies that involved participants of all ages had a pooled prevalence of 12% (95% CI: 4–24) for HAdV, 9% (95% CI: 5–14) for HRSV, and 9% (95% CI: 6–12) for HPIV. Studies performed in Kenya reported prevalence of 14% (95% CI: 7–25), 10% (95% CI: 6–15), and 9% (95% CI: 7–11) for HAdV, HRSV, and HPIV respectively.

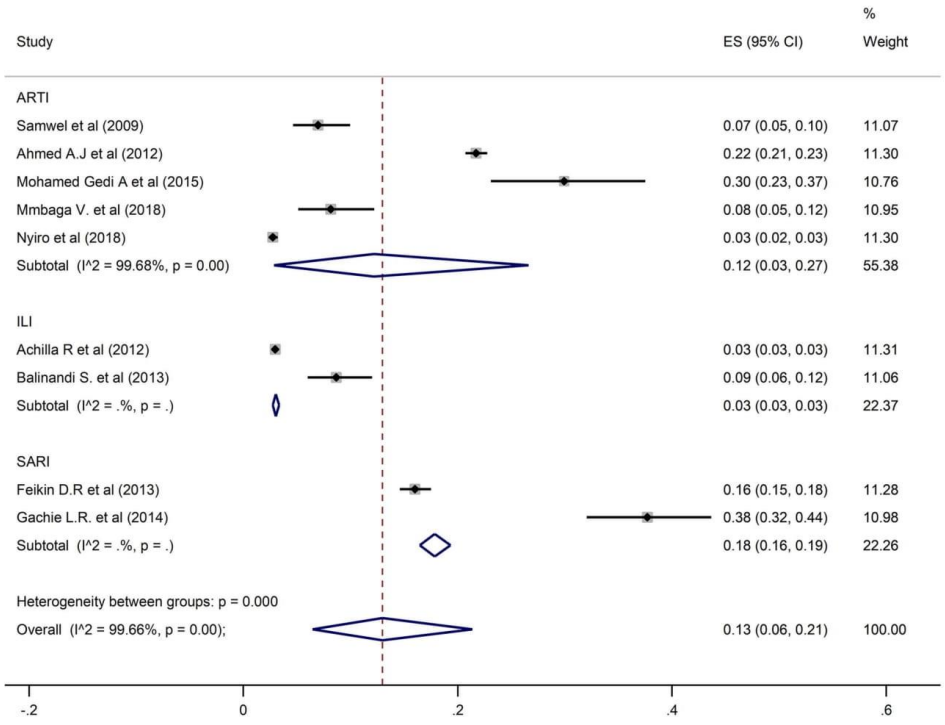

Fig 4. Pooled prevalence of human adenoviruses in ARTIs, ILI, and SARI.

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Discussion

Most of the EAC partner states have, in collaboration with WHO, established programs for surveillance for ILI and/or SARI in order to strengthen global health security under the 2005 IHR. Kenya was the first country to initiate an influenza surveillance program in 2006, followed by Uganda (2007), Rwanda (2008), and Tanzania (2009) [40, 41]. There is no known surveillance program in South Sudan or Burundi [16]. In this systematic review and meta-analysis, only data from Kenya, Tanzania, and Uganda were available.

The overall pooled prevalence of HRSV was 11%, 9% for HPIV and 13% for HAdV, but there was substantial heterogeneity by severity of illness, age group, and location. Overall, most (80%) of the reported studies were done in Kenya. Most studies were assessed as low risk for bias, and no publication bias was evident.

In this meta-analysis, the overall prevalence of HAdV was 13%. This prevalence is slightly higher than the 9.8% reported in individual studies in the Eastern Mediterranean region [42]. A study conducted in 2017 by Niang *et al.* [13] in Senegal reported 30.8% of HAdV prevalence in people with ILI. This is much higher than the 3% recorded in this review among cases of ILI. In contrast, we obtained a pooled prevalence of 30% of HAdV in individuals of five years and above. This figure is higher than the 15% reported by Holly *et al.* [43] in 2018 among

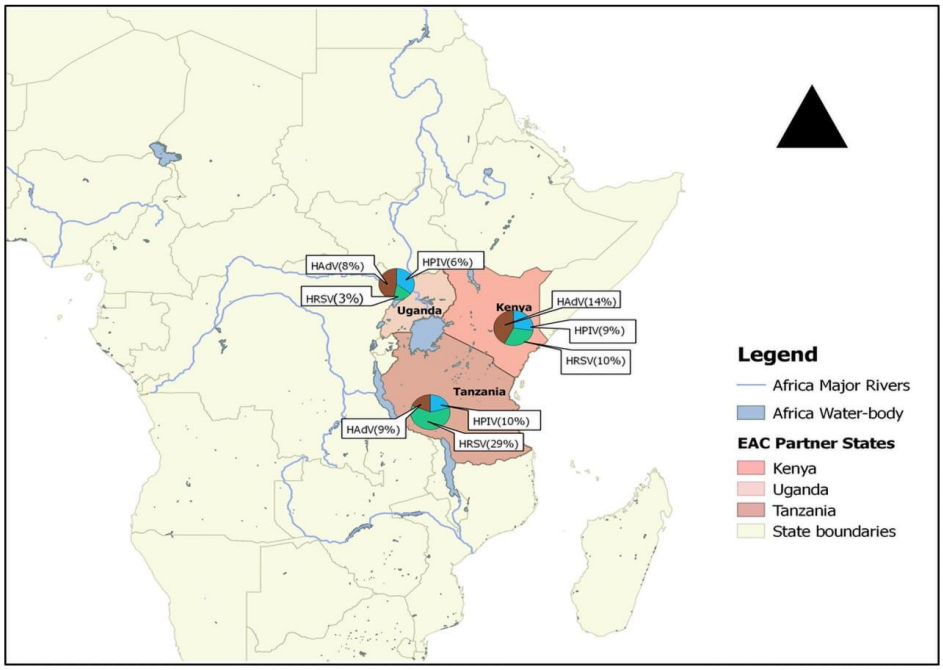

Fig 5. Distribution of HRSV, HPIV and HAdV in three EAC states between 2007 and 2020.

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college students in the United States. Moreover, our study found that those under five years had a 15% HAdV prevalence, whereas a study conducted in India among children with SARI found a HAdV prevalence of 8.8% [44]. The differences in prevalence seen between studies is likely attributable in large part to the heterogeneity in the study populations according to severity, age, and location. The variation in prevalence may also be due to of the small number of studies included in this systematic review, the methodology of sampling, or the different diagnostic tests used in the various studies.

In this systematic review, the pooled prevalence of HRSV was 11%, which is similar to a previous estimate of 14.6% among people with ARTIs in Africa [15]. In a 2015 review, the pooled HRSV prevalence among patients with ARTI in China was estimated at 18.7% [45], which was higher than that reported in our meta-analysis. In the same review, the prevalence of HRSV was 22% among SARI patients, which was the same as our results in that population [45]. However, while the study from China demonstrated a higher prevalence among infants (26.5%), our data found the same HRSV prevalence among those under five and those five-years and above (10%).

The overall prevalence of HPIV in this review was 9%. Previous studies have reported generally similar prevalence estimates of HPIV. In Cameroon, HPIV prevalence of 7.5% was reported in 2012 among ILI patients [46], which was slightly higher than the 5% prevalence found among ILI patients in this review. A slightly lower HPIV prevalence estimate of 3.2% has been reported in Latin America [47]. Our analysis found an HPIV prevalence of 16%

Table 2. Summary statistics of selected respiratory viruses' prevalence.

Outcome	HRSV							
Groups	**Studies (n)**	**Cases (n)**	**Pop (N)**	**Crude Prev. (95%CI)**	**Pooled Prev. (95%CI)**	**I^2 (%)**	**P-value (Egger)**	**P-value (hetero-geneity)**
Overall	10	2358	22627	10 (10–11)	11 (7–15)	98.87	0.618	<**0.0001**
Syndromes								
ARTIs	6	1685	18619	9 (8–9)	10 (6–15)	98.8	0.654	<**0.0001**
ILI	2	69	1230	5 (4–7)	5 (4–7)			
SARI	2	604	2778	22 (20–23)	22 (20–23)			
Age								
All age	5	1641	18456	9 (8–9)	9 (5–14)	98.94	0.914	<**0.0001**
Under Five	3	626	3746	16 (15–18)	10 (2–24)			
Five and above	1	16	168	9 (5–15)	10 (6–15)	-	-	-
Locality								
Kenya	8	2271	22001	10 (10–11)	10 (6–15)	99	0.763	<**0.0001**
Tanzania	1	75	257	29 (23–35)	29 (24–35)	-	-	-
Uganda	1	12	369	3 (1–5)	3 (2–6)	-	-	-
	HPIV							
Overall	8	1905	28363	7 (6–7)	9 (7–11)	95.4	0.179	<**0.0001**
Syndromes								
ARTIs	5	1037	12723	8 (7–8)	9 (7–11)	90.7	0.681	<**0.0001**
ILI	2	823	15359	5	5 (5–6)			
SARI	1	45	281	16 (12–20)	16 (12–21)	-	-	-
Age								
All age	4	1029	12561	8 (8–9)	9 (6–12)	94.3	0.706	<**0.0001**
Under five	1	25	388	6 (4–9)	6 (4–9)	-	-	-
Five and above	1	24	167	14 (9–21)	14 (9–21)	-	-	-
Locality								
Kenya	6	1857	27737	6 (6–7)	9 (7–11)	96.6	0.205	<**0.0001**
Tanzania	1	26	257	10 (7–14)	10 (7–14)	-	-	-
Uganda	1	22	369	6 (4–9	6 (4–9)	-	-	-
	HAdV							
Overall	9	2537	28829	9 (8–9)	13 (6–21)	99.66	0.337	<**0.0001**
Syndromes								
ARTIs	5	1614	12723	13 (12–13)	12 (3–27)	99.68	0.994	<**0.0001**
ILI	2	417	13328	3	3 (3–3.5)			
SARI	2	506	2778	18 (17–20)	18 (16–19)			
Age								
All age	5	2039	25520	8 (7–8)	12 (4–24)	99.8	0.516	<**0.0001**
Under Five	2	427	2885	15 (13–16)	15 (13–16)			
Five and above	1	50	167	30 (23–37)	30 (23–37)	-	-	-
Locality								
Kenya	7	2484	28203	9 (8–9)	14 (7–25)	99.74	0.307	<**0.0001**
Tanzania	1	21	257	8 (5–12)	8 (5–12)	-	-	-
Uganda	1	32	369	9 (6–12)	9 (6–12)	-	-	-

N: population, prev.: prevalence, CI: confidence interval, I^2 (index value): the variation in effect sizes attributable to heterogeneity, P: probability value, ARTI = acute respiratory tract infection, ILI = influenza-like illness, SARI = severe acute respiratory illness, HRSV = human respiratory syncytial virus, HPIV = human parainfluenza virus, and HAdV = human adenovirus.

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among patients with SARI, which was higher than that reported among similar patients in China (4.8%) [48]. The higher prevalence of HPIV we found among patients aged five years and above supports previous findings of higher HPIV prevalence among older age groups [49–52].

This systematic review is subject to several limitations. The systematic searches performed in this review were limited to the most accessible and widely used databases of medical literature, including Medline and Global Index Medicus. In addition, the search was complemented with unpublished literature from major public health institutions and research programs in the EAC. We identified several significant sources of heterogeneity in the estimates of pooled prevalence of HRSV, HPIV, and HAdV, including disease severity, age group, and location. Heterogeneity may also be influenced by other factors, including measured factors such as the length of the study period, study design, and laboratory technique. For example, while most studies used highly sensitive and specific diagnostic PCR tests to detect these viruses, studies which used less sensitive diagnostic methods likely underestimated prevalence. Heterogeneity may also have been influenced by unmeasured factors. Selection of participants may also have been different among the studies, likely resulting in higher prevalence among studies in which patients with more severe illness were enrolled, such as SARI as compared to ILI patients. Additionally, the sample size of studies eligible for inclusion in this analysis was small, limiting the power to detect differences, particularly in subgroup analysis. For example, not all countries of the EAC were represented, and Tanzania and Uganda only had one study each. The small sample size may be due to various factors including limited funding, government policy and priorities, the challenges of information sharing, lack of documentation, inaccessibility of databases, and difficulties with publication of data. Further, the presence of extreme values of prevalence introduced computational complexity which limited our ability to report confidence intervals for the I^2 values.

Finally, this review only included studies in which patients were selected based on defined medical conditions such as ILI and SARI or ARTIs in general. Studies that included asymptomatic participants were excluded. Asymptomatic patients would likely have had lower prevalence of these viruses than the symptomatic populations used in our study. Therefore the results of this review cannot be generalized to the general population. The exclusion of asymptomatic cases was considered necessary to avoid overdiagnosis of patients who were colonized or carriers of viruses which may not have ever caused disease.

Despite these limitations of the study, this study had several strengths. We have documented the first systematic review and use of meta-analysis to estimate the pooled prevalence of selected non-influenza viruses in the EAC. This systematic review and meta-analysis simultaneously reported HRSV, HPIV, and HAdV prevalence with a pre-defined protocol, used robust search strategies, and involved two independent investigators. Selected studies were all assessed for well-defined study characteristics to assess study heterogeneity and bias. There was no significant publication bias detected, and most of the included studies had a low risk of study bias. Sensitivity analysis yielded similar results to crude estimates, further supporting the robustness of this systematic review and meta-analysis.

Conclusions and recommendations

Respiratory illness surveillance programs in the EAC have enhanced the detection of both influenza and non-influenza viruses for over a decade. However, there are no platforms for systematic information sharing in the region. It is vital to establish national and regional information-sharing platforms for non-influenza respiratory viruses to guide future research, policy, and development. Our findings indicate that human adenoviruses are the most common

sources of ILI and SARI other than influenza infection, followed by the human respiratory syncytial virus and parainfluenza virus. Future studies or research could identify the prevalence of HRSV, HPIV, and HAdV using standardized methods and populations to increase comparability among studies and to account for sources of misclassification and heterogeneity. Additional studies should be considered among older populations, among populations from EAC countries from which no data were found, and asymptomatic populations. In addition, the literature search could include additional databases used in biomedical research. Finally, other emerging respiratory pathogens could be studied and further molecular characterization could be carried out to assess transmission.

Supporting information

S1 File. Search strategies.
(PDF)

S2 File. PRISMA checklist.
(PDF)

S3 File. List of individual study characteristics.
(TIF)

S4 File. Individual study bias assessment.
(PDF)

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References

1. WHO | Battle against Respiratory Viruses (BRaVe) initiative [Internet]. WHO. [cited 2018 Mar 5]. http://www.who.int/influenza/patient_care/clinical/brave/en/
2. McIntosh K. Community-Acquired Pneumonia in Children. New England Journal of Medicine. 2002 Feb 7; 346(6):429–37. https://doi.org/10.1056/NEJMra011994 PMID: 11832532
3. Piedimonte G, Perez M. Respiratory Syncytial Virus Infection and Bronchiolitis. Pediatrics in review / American Academy of Pediatrics. 2014 Dec 1; 35:519–30. https://doi.org/10.1542/pir.35-12-519 PMID: 25452661
4. Merckx J, Ducharme FM, Martineau C, Zemek R, Gravel J, Chalut D, et al. Respiratory Viruses and Treatment Failure in Children With Asthma Exacerbation. Pediatrics. 2018 Jun 4;e20174105. https://doi.org/10.1542/peds.2017-4105 PMID: 29866794
5. Duenas Meza E, Jaramillo CA, Correa E, Torres-Duque CA, García C, González M, et al. Virus and Mycoplasma pneumoniae prevalence in a selected pediatric population with acute asthma exacerbation. J Asthma. 2016; 53(3):253–60. https://doi.org/10.3109/02770903.2015.1075548 PMID: 26799194
6. Ziegler T, Mamahit A, Cox NJ. 65 years of influenza surveillance by a World Health Organization-coordinated global network. Influenza Other Respir Viruses. 2018 May 4; https://doi.org/10.1111/irv.12570 PMID: 29727518
7. Tang JW, Lam TT, Zaraket H, Lipkin WI, Drews SJ, Hatchette TF, et al. Global epidemiology of non-influenza RNA respiratory viruses: data gaps and a growing need for surveillance. The Lancet Infectious Diseases. 2017 Oct 1; 17(10):e320–6. https://doi.org/10.1016/S1473-3099(17)30238-4 PMID: 28457597
8. Fernandes-Matano L, Monroy-Muñoz IE, Angeles-Martínez J, Sarquiz-Martinez B, Palomec-Nava ID, Pardavé-Alejandre HD, et al. Prevalence of non-influenza respiratory viruses in acute respiratory infection cases in Mexico. PLoS One [Internet]. 2017 May 3 [cited 2018 Dec 17]; 12(5). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5415110/ https://doi.org/10.1371/journal.pone.0176298 PMID: 28467515
9. Manjarrez-Zavala ME, Rosete-Olvera DP, Gutiérrez-González LH, Ocadiz-Delgado R, Cabello-Gutiérrez C. Pathogenesis of Viral Respiratory Infection. 2013 [cited 2018 Jan 15]; Available from: http://www.intechopen.com/books/respiratory-disease-and-infection-a-new-insight/pathogenesis-of-viral-respiratory-infection
10. Fendrick AM, Monto AS, Nightengale B, Sarnes M. The Economic Burden of Non–Influenza-Related Viral Respiratory Tract Infection in the United States. Arch Intern Med. 2003 Feb 24; 163(4):487–94. https://doi.org/10.1001/archinte.163.4.487 PMID: 12588210
11. Shi T, McAllister DA, O'Brien KL, Simoes EAF, Madhi SA, Gessner BD, et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in young children in 2015: a systematic review and modelling study. Lancet. 2017 Sep 2; 390 (10098):946–58. https://doi.org/10.1016/S0140-6736(17)30938-8 PMID: 28689664
12. Ho A. Viral pneumonia in adults and older children in sub-Saharan Africa—epidemiology, aetiology, diagnosis and management. Pneumonia. 2014 Dec 1; 5(1):18–29. https://doi.org/10.15172/pneu.2014.5/446 PMID: 31641571
13. Niang MN, Diop NS, Fall A, Kiori DE, Sarr FD, Sy S, et al. Respiratory viruses in patients with influenza-like illness in Senegal: Focus on human respiratory adenoviruses. PLoS ONE. 2017; 12(3):e0174287. https://doi.org/10.1371/journal.pone.0174287 PMID: 28328944
14. Moumouni Sanou A, Cissé A, Rodolphe Millogo T, Sagna T, Tialla D, Williams T, et al. EC MICROBIOLOGY Review Article Systematic Review of Articles on Etiologies of Acute Respiratory Infections in Children Aged Less Than Five Years in Sub-Saharan Africa, 2000–2015. 2016 Oct 6; 36:556–71.

15. Kenmoe S, Bigna JJ, Well EA, Simo FBN, Penlap VB, Vabret A, et al. Prevalence of human respiratory syncytial virus infection in people with acute respiratory tract infections in Africa: A systematic review and meta-analysis. Influenza Other Respir Viruses. 2018 Jun 16; https://doi.org/10.1111/irv.12584 PMID: 29908103

16. Sanicas M, Forleo E, Pozzi G, Diop D. A review of the surveillance systems of influenza in selected countries in the tropical region. Pan Afr Med J [Internet]. 2014 Oct 1 [cited 2018 Oct 31]; 19. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4341259/ https://doi.org/10.11604/pamj.2014.19.121.4280 PMID: 25745529

17. Overview of EAC [Internet]. [cited 2018 Nov 1]. https://www.eac.int/overview-of-eac

18. MacPherson DW, Gushulak BD, Macdonald L. Health and foreign policy: influences of migration and population mobility. Bull World Health Organ. 2007 Mar; 85(3):200–6. https://doi.org/10.2471/blt.06.036962 PMID: 17486211

19. Hammitt LL, Kazungu S, Morpeth SC, Gibson DG, Mvera B, Brent AJ, et al. A preliminary study of pneumonia etiology among hospitalized children in Kenya. Clin Infect Dis. 2012 Apr; 54 Suppl 2:S190–199. https://doi.org/10.1093/cid/cir1071 PMID: 22403235

20. O'Meara WP, Mott JA, Laktabai J, Wamburu K, Fields B, Armstrong J, et al. Etiology of pediatric fever in western Kenya: a case-control study of falciparum malaria, respiratory viruses, and streptococcal pharyngitis. Am J Trop Med Hyg. 2015 May; 92(5):1030–7. https://doi.org/10.4269/ajtmh.14-0560 PMID: 25758648

21. Berkley JA, Munywoki P, Ngama M, Kazungu S, Abwao J, Bett A, et al. Viral Etiology of Severe Pneumonia Among Kenyan Infants and Children. JAMA. 2010 May 26; 303(20):2051–7. https://doi.org/10.1001/jama.2010.675 PMID: 20501927

22. Enan Khalid A., Nabeshima Takeshi, Kubo Toru, Buerano Corazon C., El Hussein Abdel Rahim M., Elkhidir Isam M., et al. Survey of causative agents for acute respiratory infections among patients in Khartoum-State, Sudan, 2010–2011. Virol J. 2013 Oct 25; 10:312. https://doi.org/10.1186/1743-422X-10-312 PMID: 24160894

23. Lutwama JJ, Bakamutumaho B, Kayiwa JT, Chiiza R, Namagambo B, Katz MA, et al. Clinic- and hospital-based sentinel influenza surveillance, Uganda 2007–2010. J Infect Dis. 2012 Dec 15; 206 Suppl 1: S87–93. https://doi.org/10.1093/infdis/jis578 PMID: 23169978

24. Kenmoe S, Bigna JJ, Well EA, Simo FBN, Penlap VB, Vabret A, et al. Prevalence of human respiratory syncytial virus infection in people with acute respiratory tract infections in Africa: A systematic review and meta-analysis. Influenza and Other Respiratory Viruses. 2018 Nov 1; 12(6):793–803. https://doi.org/10.1111/irv.12584 PMID: 29908103

25. Lefebvre A, Manoha C, Bour J-B, Abbas R, Fournel I, Tiv M, et al. Human metapneumovirus in patients hospitalized with acute respiratory infections: A meta-analysis. J Clin Virol. 2016 Aug; 81:68–77. https://doi.org/10.1016/j.jcv.2016.05.015 PMID: 27337518

26. Hoy D, Brooks P, Woolf A, Blyth F, March L, Bain C, et al. Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. J Clin Epidemiol. 2012 Sep; 65 (9):934–9. https://doi.org/10.1016/j.jclinepi.2011.11.014 PMID: 22742910

27. Shamliyan T, Kane RL, Dickinson S. A systematic review of tools used to assess the quality of observational studies that examine incidence or prevalence and risk factors for diseases. J Clin Epidemiol. 2010 Oct; 63(10):1061–70. https://doi.org/10.1016/j.jclinepi.2010.04.014 PMID: 20728045

28. Nyaga VN, Arbyn M, Aerts M. Metaprop: a Stata command to perform meta-analysis of binomial data. Arch Public Health [Internet]. 2014 Nov 10 [cited 2018 Nov 8]; 72. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4373114/ https://doi.org/10.1186/2049-3258-72-39 PMID: 25810908

29. Barendregt JJ, Doi SA, Lee YY, Norman RE, Vos T. Meta-analysis of prevalence. J Epidemiol Community Health. 2013 Nov 1; 67(11):974–8. https://doi.org/10.1136/jech-2013-203104 PMID: 23963506

30. Brockwell SE, Gordon IR. A comparison of statistical methods for meta-analysis. Stat Med. 2001 Mar 30; 20(6):825–40. https://doi.org/10.1002/sim.650 PMID: 11252006

31. Jackson D, Bowden J, Baker R. How does the DerSimonian and Laird procedure for random effects meta-analysis compare with its more efficient but harder to compute counterparts? Journal of Statistical Planning and Inference. 2010 Apr 1; 140(4):961–70.

32. Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods. Stat Med. 1998 Apr 30; 17(8):857–72. https://doi.org/10.1002/(sici)1097-0258(19980430)17:8<857::aid-sim777>3.0.co;2-e PMID: 9595616

33. B.Sc.1 MH, Cuijpers2 PDP, Furukawa3 PDTA, Ebert2 APDDD. Chapter 6 Between-study Heterogeneity | Doing Meta-Analysis in R [Internet]. [cited 2019 Sep 24]. https://bookdown.org/MathiasHarrer/Doing_Meta_Analysis_in_R/heterogeneity.html

34. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003 Sep 6; 327(7414):557–60. https://doi.org/10.1136/bmj.327.7414.557 PMID: 12958120

35. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002 Jun 15; 21(11):1539–58. https://doi.org/10.1002/sim.1186 PMID: 12111919

36. metametabias.pdf [Internet]. [cited 2019 Sep 24]. https://www.stata.com/manuals/metametabias.pdf

37. Lin L, Chu H, Murad MH, Hong C, Qu Z, Cole SR, et al. Empirical Comparison of Publication Bias Tests in Meta-Analysis. J GEN INTERN MED. 2018 Aug 1; 33(8):1260–7. https://doi.org/10.1007/s11606-018-4425-7 PMID: 29663281

38. Shi X, Nie C, Shi S, Wang T, Yang H, Zhou Y, et al. Effect comparison between Egger's test and Begg's test in publication bias diagnosis in meta-analyses: evidence from a pilot survey. Int J Res Stud Biosci. 2017; 5(5):14–20.

39. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997 Sep 13; 315(7109):629–34. https://doi.org/10.1136/bmj.315.7109.629 PMID: 9310563

40. Sanchez JL, Johns MC, Burke RL, Vest KG, Fukuda MM, Yoon I-K, et al. Capacity-building efforts by the AFHSC-GEIS program. BMC Public Health. 2011 Mar 4; 11(2):S4. https://doi.org/10.1186/1471-2458-11-S2-S4 PMID: 21388564

41. Nyatanyi T, Nkunda R, Rukelibuga J, Palekar R, Muhimpundu MA, Kabeja A, et al. Influenza sentinel surveillance in Rwanda, 2008–2010. J Infect Dis. 2012 Dec 15; 206 Suppl 1:S74–79. https://doi.org/10.1093/infdis/jis574 PMID: 23169976

42. Horton KC, Dueger EL, Kandeel A, Abdallat M, El-Kholy A, Al-Awaidy S, et al. Viral etiology, seasonality and severity of hospitalized patients with severe acute respiratory infections in the Eastern Mediterranean Region, 2007–2014. PLoS ONE. 2017; 12(7):e0180954. https://doi.org/10.1371/journal.pone.0180954 PMID: 28704440

43. Biggs HM, Lu X, Dettinger L, Sakthivel S, Watson JT, Boktor SW. Adenovirus-Associated Influenza-Like Illness among College Students, Pennsylvania, USA. Emerg Infect Dis. 2018 Nov; 24(11):2117–9. https://doi.org/10.3201/eid2411.180488 PMID: 30334721

44. Malhotra B, Swamy MA, Janardhan Reddy PV, Gupta ML. Viruses causing severe acute respiratory infections (SARI) in children ≤5 years of age at a tertiary care hospital in Rajasthan, India. Indian J Med Res. 2016 Dec; 144(6):877–85. https://doi.org/10.4103/ijmr.IJMR_22_15 PMID: 28474624

45. Zhang Y, Yuan L, Zhang Y, Zhang X, Zheng M, Kyaw MH. Burden of respiratory syncytial virus infections in China: Systematic review and meta-analysis. J Glob Health. 2015 Dec; 5(2):020417. https://doi.org/10.7189/jogh.05.020417 PMID: 26682049

46. Njouom R, Yekwa EL, Cappy P, Vabret A, Boisier P, Rousset D. Viral etiology of influenza-like illnesses in Cameroon, January-December 2009. J Infect Dis. 2012 Dec 15; 206 Suppl 1:S29–35.

47. Villaran MV, García J, Gomez J, Arango AE, Gonzales M, Chicaiza W, et al. Human parainfluenza virus in patients with influenza-like illness from Central and South America during 2006–2010. Influenza Other Respir Viruses. 2014 Mar; 8(2):217–27. https://doi.org/10.1111/irv.12211 PMID: 24286248

48. Feng L, Li Z, Zhao S, Nair H, Lai S, Xu W, et al. Viral Etiologies of Hospitalized Acute Lower Respiratory Infection Patients in China, 2009–2013. PLOS ONE. 2014 Jun 19; 9(6):e99419. https://doi.org/10.1371/journal.pone.0099419 PMID: 24945280

49. Feikin Daniel R., Njenga M. Kariuki, Bigogo Godfrey, Aura Barrack, Aol George, Audi Allan, et al. Etiology and Incidence of viral and bacterial acute respiratory illness among older children and adults in rural western Kenya, 2007–2010. PLoS ONE. 2012; 7(8):e43656. https://doi.org/10.1371/journal.pone.0043656 PMID: 22937071

50. Uchi Nyiro Joyce, Munywoki Patrick, Kamau Everlyn, Agoti Charles, Gichuki Alex, Etyang Timothy, et al. Surveillance of respiratory viruses in the outpatient setting in rural coastal Kenya: baseline epidemiological observations. Wellcome Open Res. 2018; 3:89. https://doi.org/10.12688/wellcomeopenres.14662.1 PMID: 30175247

51. Balinandi Stephen, Bakamutumaho Barnabas, Kayiwa John T., Ongus Juliette, Oundo Joseph, Awor Anna C., et al. The viral aetiology of influenza-like illnesses in Kampala and Entebbe, Uganda, 2008. Afr J Lab Med [Internet]. 2013 Jun 24 [cited 2018 Sep 28]; 2(1). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5637772/

52. Mohamed Gedi A., Ahmed Jamal A., Marano Nina, Mohamed Abdinoor, Moturi Edna, Burton Wagacha, et al. Etiology and Incidence of Viral Acute Respiratory Infections Among Refugees Aged 5 Years and Older in Hagadera Camp, Dadaab, Kenya. Am J Trop Med Hyg. 2015 Dec; 93 (6):1371–6. https://doi.org/10.4269/ajtmh.15-0141 PMID: 26458776

Annex 18: List of under peer-review manuscripts

IJID Regions

Morbidity burden, seasonality and factors associated with the respiratory syncytial virus, parainfluenza virus, and Adenovirus infections in Kenya

--Manuscript Draft--

Manuscript Number:	
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Abstract:	Background Human respiratory syncytial viruses (HRSV), human parainfluenza viruses (HPIV), and human Adenoviruses (HAdV) cause a substantial morbidity burden globally. Objective The study sought to estimate morbidity burden, assess seasonality, and determine factors associated with these respiratory viruses among the Kenyan population. Methods The data was obtained from Kenyan sites located in the present Köppen-Geiger climate classification system. By descriptive analysis, we defined proportion of morbidity burden, visualized time-series data from January 2007-December 2013. Logistic regression was used to identify the factors associated with infection outcome. Results The morbidity burden for HRSV was 3.1%, HPIV 5.3%, and HAdV 3.3%. Infants were more likely to be infected with these viruses compared to other age groups. HRSV exhibited seasonality with high occurrence in January-March (Odds Ratio [OR] =2.73) and April-June (OR=3.01). Hot land surface temperature (≥40°C) was also associated with HRSV infections (OR=2.75), as was warmer air temperature (19-22.9°C) (OR=1.68) compared to cooler air temperature (<19°C). Moderate rainfall (150-200mm) areas had greater odds of HSRV infection (OR=1.32) than low rainfall (<150mm). Conclusion HRSV, HPIV, and HAdVs contributed to morbidity burden, and infants were significantly affected. HRSV had a clear seasonal pattern and were associated with climate parameters, contrary to HPIV and HAdVs.
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Title: Spatial and Spatio-Temporal Distribution of Human Respiratory Syncytial Virus, Human Parainfluenza Virus, and Human Adenoviruses Cases in Kenya 2007-2013

Short title: Spatial and Spatio-temporal analysis of selected respiratory viruses in Kenya

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Abstract

Background: Human respiratory syncytial virus (HRSV), human parainfluenza virus (HPIV), and human adenovirus (HAdV) epidemics differ in geographical location, time, and virus type. Regions prone to infections can be identified using geographic information systems (GIS) and available methods for detecting spatial and time clusters. We sought to find statistically significant spatial and time clusters of HRSV, HPIV, and HAdV cases in different parts of Kenya.

Methods: To analyze retrospective data, we used a geographical information system (GIS) and the spatial scan statistic. The information was gathered from surveillance sites and aggregated at the county level in order to identify purely spatial and Spatio-temporal clusters. To detect the presence of spatial autocorrelation, the local Moran's I test was used. To detect the spatial clusters of HRSV, HPIV, and HAdV cases, we performed the purely spatial scan statistic. Furthermore, space-time clusters were identified using space-time scan statistics. Both spatial and space-time analyses were based on the discrete Poisson model with a statistical significance of $p<0.005$

Results: The findings showed that HRSV, HPIV, and HAdV cases had significant autocorrelation within the study areas. Furthermore, in the Western region of the country, the three respiratory viruses had local clusters with significant positive autocorrelation ($p<0.05$). Statistically, the Western region had the significant purely spatial clusters of HRSV, HPIV, and HAdV occurrence. Furthermore, the space-time analysis revealed that the HPIV primary cluster persisted in the Western region from 2007 to 2013. However, primary clusters of HRSV and HAdV were observed in the Coastal region in 2009-11 and 2008-09, respectively.

Conclusion: According to the findings of this study, RSV, HPIV, and HAdV hotspots (clusters) occurred in Kenya's Western and Coastal regions from 2007 to 2013. Regardless of time, the Western region appeared to be more prone to the occurrence of the three respiratory viruses.

Keywords: Surveillance, spatial, space-time, Scan statistics, HRSV, HPIV, HAdV