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The Epidemiology and Burden of Influenza B/Victoria and B/Yamagata Lineages in Kenya, 2012–2016

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Background. The impact of influenza B virus circulation in Sub-Saharan Africa is not well described.

Methods. We analyzed data from acute respiratory illness (ARI) in Kenya. We assessed clinical features and age-specific hospitalization and outpatient visit rates by person-years for influenza B/Victoria and B/Yamagata and the extent to which circulating influenza B lineages in Kenya matched the vaccine strain component of the corresponding season (based on Northern Hemisphere [October–March] and Southern Hemisphere [April–September] vaccine availability).

Results. From 2012 to 2016, influenza B represented 31% of all influenza-associated ARIs detected (annual range, 13–61%). Rates of influenza B hospitalization and outpatient visits were higher for <5 vs ≥5 years. Among <5 years, B/Victoria was associated with pneumonia hospitalization (64% vs 44%; $P = .010$) and in-hospital mortality (6% vs 0%; $P = .042$) compared with B/Yamagata, although the mean annual hospitalization rate for B/Victoria was comparable to that estimated for B/Yamagata. The 2 lineages co-circulated, and there were mismatches with available trivalent influenza vaccines in 2/9 seasons assessed.

Conclusions. Influenza B causes substantial burden in Kenya, particularly among children aged <5 years, in whom B/Victoria may be associated with increased severity. Our findings suggest a benefit from including both lineages when considering influenza vaccination in Kenya.

Keywords. burden; hospitalization; incidence; influenza B; Kenya; lineage; Victoria; Yamagata.

Two subtypes of influenza A (H1N1pdm09, H3N2) and 2 influenza B lineages (B/Victoria and B/Yamagata) currently circulate in humans and cause disease annually. Whereas studies have shown that influenza A is associated with a relatively higher burden of disease [1–3], the clinical presentations of the 2 influenza virus types (A and B) seem to be comparable [4, 5], and some studies have shown influenza B to lead to severe complications and even death [6–8].

Several studies suggest that B/Victoria and B/Yamagata generally co-circulate [2, 9, 10]. Inclusion of only 1 lineage in vaccine formulation may adversely affect vaccine effectiveness because of the limited cross-protection among the 2 B lineages when there is a mismatch between what is circulating and what is included in the vaccine [11, 12]. These factors have led countries to include quadrivalent influenza vaccine (QIV), with both B lineages, to their annual influenza vaccine recommendation [13, 14]. The QIV has been shown to reduce influenza-associated burden and may be cost-effective compared with the trivalent influenza vaccine (TIV), which contains 1 of the 2 lineage types [15–18]. However, TIV is still the only option available in some countries.

In Kenya, influenza circulates throughout the year without distinct seasonality but causing substantial disease burden in the population, particularly among children aged <5 years [19–22]. Nonetheless, there are limited Kenyan data describing the epidemiological and clinical aspects of influenza A and B separately and no data describing the 2 B lineages. Currently, there is no national influenza vaccination program in Kenya, but a recent study suggested that either of the vaccine formulations, Northern Hemisphere (NH) or Southern Hemisphere (SH), could be suitable for use if a vaccination program is implemented [23]. In 2016, the Kenyan National Immunization Technical Advisory Group (KENITAG) issued a provisional recommendation for the use of influenza vaccination among children 6–23 months of age. Information on the impact of influenza B in Kenya will be important to policy- and decision-makers when considering implementation of an influenza vaccination program, especially regarding which vaccine to use (TIV is the only formulation currently licensed and available in the country). Here, we describe the epidemiology and clinical presentation associated with influenza B virus lineages (B/Victoria and B/Yamagata) among medically attended cases of acute respiratory illness (ARI) in Kenya.

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METHODS

Study Sites

We analyzed data from January 2012 to December 2016 from 8 inpatient sites (Siaya County Referral Hospital [CRH], Kenyatta National Hospital [KNH], Mombasa CRH, Kakamega CRH, Nakuru CRH, Nyeri CRH, and Kakuma and Dadaab refugee camps), 2 outpatient sites (Ting'wang'i Health Center and Tabitha Clinic), and 1 site that contributed data for both in- and outpatients (Saint Elizabeth Lwak Mission Hospital [LMH]) (Figure 1).

Two of the surveillance sites are located within the Health and Demographic Surveillance System (HDSS) platform in Western Kenya and allowed for generation of disease burden estimates [19, 24–26]. Briefly, Siaya CRH is located within the Karemo area of Siaya County and has an estimated catchment population of 80 000. LMH is located within Asembo area of the same county and has a catchment population of approximately 25 000. These 2 surveillance sites were used to estimate hospitalization and outpatient visit rates, respectively, because of the availability of age-specific denominator data.

Data Collection and Case Definitions

From Monday to Friday, trained surveillance officers identified patients at each site who were admitted with respiratory illness on the same day (or the day before) and assessed their eligibility for inclusion in the surveillance platform. Patients admitted on Saturday were enrolled on Monday if eligibility was met. Outpatients were enrolled on the day of clinic visitation. The surveillance case definition varied with surveillance platform. For the outpatient settings (at Ting'wang'i Health Center, Tabitha Clinic, and LMH), influenza-like-illness (ILI) was defined as an acute onset of illness (within the last 14 days), axillary temperature ≥38°C, and cough or sore throat in an outpatient of any age [24, 26]. At LMH and Tabitha Clinic, patients were additionally assessed on whether they had acute lower respiratory illness (ALRI). Among children age <5 years, ALRI was defined as acute onset of illness (within the last 14 days) with cough or difficulty breathing and at least 1 of the following: lower chest wall in-drawing, stridor, oxygen saturation <90%, inability to drink or breastfeed, vomiting everything, convulsions, lethargy, or unconsciousness [26]. For patients ≥5 years, ALRI was defined as acute onset of illness (within the last 14 days) with cough or difficulty breathing or chest pain and a recorded axillary temperature of ≥38°C or oxygen saturation level of <90% [26]. The same ALRI case definition was used for outpatients at Tabitha Clinic and both inpatients and outpatients at LMH). Depending on clinician assessment of ALRI cases, patients could be managed clinically as outpatients or referred to hospital admission.

For all other sites, severe acute respiratory illness (SARI) was defined as an acute onset of illness (within the last 14 days) among patients who were hospitalized with cough and reported fever (feverishness) or a recorded temperature of ≥38°C. Patients who met the various case definitions (depending on surveillance site) had a structured questionnaire administered by the surveillance officer to collect demographics, underlying diseases, and signs and symptoms, and were also assessed by study clinicians on physical and clinical findings. For those hospitalized, chart review was also done at the time of discharge or death to collect clinical outcome data.

Laboratory Testing for Influenza

Patients who met criteria for respiratory sampling were asked for verbal consent (or written consent for patients at LMH and Tabitha Clinic) to have nasopharyngeal (NP) and oropharyngeal (OP) swabs collected on the day of enrollment. At the sentinel hospital surveillance sites, only SARI cases enrolled from Monday through Wednesday had NP/OP swabs collected [26, 27]. The NP/OP swabs were combined into a single tube with viral transport media (VTM) and immediately refrigerated at 2°C–8°C before transportation to the Centers for Disease Control and Prevention (CDC)–supported Kenya Medical Research Institute (KEMRI) laboratories in Kisumu and Nairobi for testing. Total nucleic acids were extracted from the NP/OP swabs using MagNA Pure 96 DNA and the Viral NA Small Volume Kit and MagNA Pure 96 Instrument (Roche). The extracted nucleic acids were amplified in a 1-step real-time reverse transcription polymerase chain reaction (rRT-PCR) with primers and probes specific to the influenza A and B viruses using the AgPath-ID 1-step RT-PCR kit (Applied Biosystems Foster City, CA). Samples that tested positive for influenza B were further tested for the lineage types (B/Victoria and B/Yamagata) using specific primers and probes, per the US CDC protocol for detection and characterization of influenza B genotypes. The cycling conditions used were reverse transcription at 45°C for 10 minutes, enzyme activation at 95°C for 10 minutes, and 45 cycles of 95°C for 15 seconds and 55°C for 1 minute.

Data Analyses

For this analysis, patients who met the case definitions listed above were further classified as having pneumonia if they presented with cough or difficulty breathing and any 1 of the following: tachypnea (respiratory rate of >60/min for children <2 months, >50/min for children aged 2–11 months, and >40/min for children aged 12–59 months), chest in-drawing, or hypoxia (oxygen saturation of <90%) [25]. Patients who met the ALRI case definition and were hospitalized were included in the group of SARI cases when assessing clinical features of hospitalized patients. Weight-for-age measures for children <5 years were calculated based on the World Health Organization z-scores [28]. Data on demographics and characteristics of ARI cases were described using proportions. Continuous data were described using medians and interquartile ranges (IQRs). Data showing the temporal distribution of influenza (by type and B lineage) were presented using

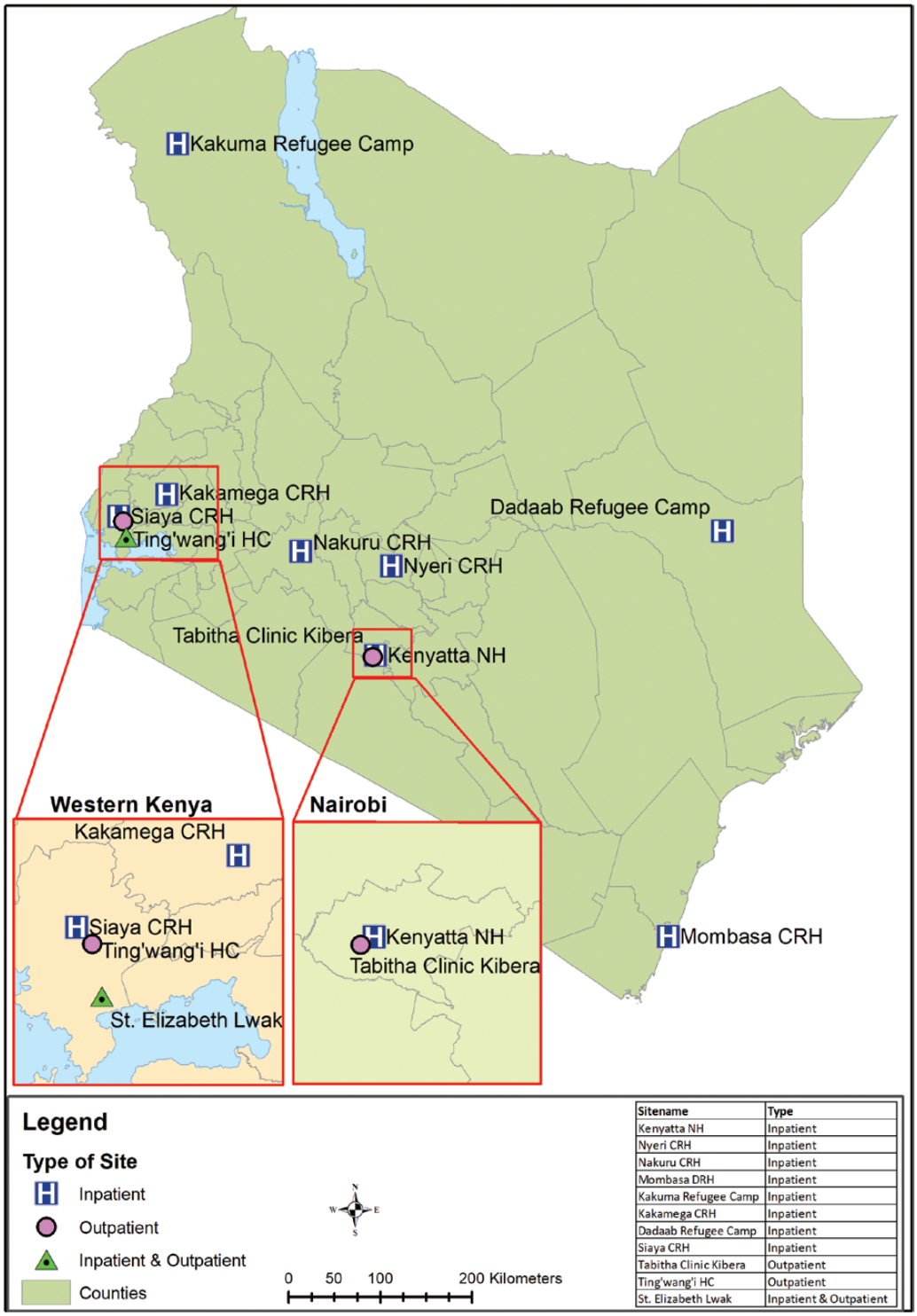

Figure 1. Map of Kenya showing the location of the influenza surveillance sites. Abbreviations: CRH, County Referral Hospital; HC, Health Center; NH, Northern Hemisphere.

line and bar graphs. Associations between patients' characteristics and influenza B lineages were assessed using chi-square or Fisher exact tests. These analyses were conducted separately for hospitalized patients and outpatients and for children <5 years and those ≥5 years.

Assessing the Match Between Circulating Influenza Lineage Types and Available TIV Vaccines

To assess the extent to which circulating influenza B lineages in Kenya were matched to the vaccine strain component included for the corresponding season [29], we created 9 separate

seasons that corresponded to the time of the year when NH (October to March), and SH (April to September) vaccines were available. We calculated the proportion of B/Victoria and B/Yamagata that were circulating over these specific time periods and defined a mismatched season as when >50% of circulating lineages differed from the vaccine strain component of the TIV available. We also defined influenza co-circulation seasons (NH or SH) as periods when >10% of the 2 lineages were detected.

Calculating Rates of Hospitalizations and Outpatient Visits Associated With Influenza A and B

Annual rates of SARI hospitalization associated with influenza A and B and influenza B/Victoria and B/Yamagata were calculated using data collected from Siaya CRH and using methods previously described [19, 24]. Briefly, the annual age-specific (<5 years, and ≥5 years) incidence of hospitalized SARI that was associated with the 2 influenza types and B lineages was calculated by dividing the age-specific number of laboratory-confirmed cases who were residents in the hospital catchment area by the age-specific person-years calculated from all of the residents at risk in the hospital's catchment area.

Rates of outpatient visits associated with influenza A and B and influenza B/Victoria and B/Yamagata were estimated using methods similar to those described above. However, the data used were collected from the LMH outpatient clinic. The age-specific incidence of outpatient visits associated with influenza A and B, and with each of the influenza B lineages, were calculated by dividing the number of laboratory-confirmed cases among ILI cases by the age-specific person-years calculated from catchment area residents. We chose to present outpatient rates from LMH because LMH is in the same county as Siaya CRH (ie, hospitalization data), which would allow us to compare hospitalized and outpatient rates from a similar setting and population.

All of the calculated rates were adjusted for those who met the sampling criteria but were not tested for influenza. For the rates of 2 influenza type B lineages, rates were further adjusted for those who tested positive for influenza B but did not have the lineage test result (either because the test was not done or the sample could not be genotyped). All the adjustments were stratified by type of case (hospitalized and outpatient), year of enrollment, and age group. The ratio of hospitalization to outpatient visits for each influenza type (A and B) was then calculated by dividing the rate of influenza-associated hospitalizations by the rate of influenza-associated outpatient visits. Ninety-five percent confidence intervals (CIs) were calculated using the Poisson approximation method [24, 30]. All data analyses were performed using Stata, version 13.0 (Stata Corp, College Station, TX).

Ethical Considerations

The study protocols at Siaya CRH, LMH, Ting'wang'i, and Tabitha were approved by both the institutional review board of the US CDC (CDC-6543, CDC-4566) and the ethical review committee of KEMRI (SSC-2558, SSC-1899). At all other sites, the Kenya Ministry of Health (KMoH) considered sentinel surveillance for influenza as part of routine public health activities. Verbal consent (written consent for LMH and Tabitha Clinic) was obtained from all patients (or their guardians) before questionnaires were administered and specimens collected.

RESULTS

Descriptive Analyses

From 2012 through 2016, 24 268 patients with ARI were enrolled at 11 surveillance sites in Kenya and tested for influenza A and B viruses. Among these, 16 182 (67%) patients were hospitalized with SARI or ALRI and 8086 (33%) presented with ILI or ALRI and were seen as outpatients (Table 1). The majority of these patients (17 851 [74%]) were children <5 years, and 11 622 (48%) were female. Of those hospitalized, 1271 (8%) tested positive for influenza (856 [5%] for influenza A and 415 [3%] for influenza B). Among outpatients, 1374 (17%) tested positive for influenza (966 [12%] for influenza A and 408 [5%] for influenza B). Overall, of all the influenza-positive cases that were detected over the 5-year period, 31% were influenza B virus, with the highest percentage (61%) of influenza B detected in 2016 and the lowest percentage (13%) detected in 2014.

Of all the 823 influenza B cases identified over the study period, 566 (69%) were further subtyped, of which 305 (37%) were B/Victoria, 259 (31%) were B/Yamagata, and 2 patients were co-infected with B/Victoria and B/Yamagata. Influenza B cases that were genotyped differed from those that were not by type of case ($P < .001$), year of enrollment ($P = .001$), and age group ($P = .037$) but were similar otherwise (Table 1). Overall, B/Victoria predominated in 2012 and 2016, whereas B/Yamagata predominated in 2013 and 2015. There was little activity of influenza B virus in 2014 (Supplementary Figure 1).

A substantial number of pneumonia cases were associated with influenza B detection during the study period (Figure 2). In 2016, the proportion of pneumonia associated with influenza B was higher, surpassing the proportion associated with influenza A (5.7% vs 2.7%). In 2016, influenza activity was dominated by B/Victoria.

Characteristics Associated With Influenza B Lineage (B/Victoria vs B/Yamagata)

Among hospitalized children, the clinical conditions that were significantly associated with B/Victoria compared with B/Yamagata were nasal flaring (44% vs 18%; $P < .001$), chills (14% vs 1%; $P = .001$), chest wall in-drawing (48% vs 20%; $P < .001$), and hypoxia (14% vs 1%; $P = .018$) (Table 2). Influenza B/Victoria was more likely associated with pneumonia among SARI cases compared with B/Yamagata (64% vs 44%; $P = .010$) and associated with in-hospital mortality (6% vs 0%; $P = .042$). The median duration of hospitalization (IQR) was longer among children who tested positive for B/Victoria (4 [2–7]

Table 1. Demographic Characteristics of Participants Tested for Influenza A and B From 11 Surveillance Sites in Kenya, 2012–2016

Variable	Tested for Influenza A/B	Influenza A Positives	Influenza B Positives	Influenza B Genotyped	Influenza B not Genotyped	Comparison of Cases With and Without Genotype Data[b]
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	*P* Value
All	24 268 (100.0)	1822 (100.0)	823 (100.0)	566 (100.0)	257 (100.0)	-
Hospitalized	16 182 (66.7)	856 (47.0)	415 (50.4)	245 (43.3)	170 (66.1)	<.001
Outpatient	8086 (33.3)	966 (53.0)	408 (49.6)	321 (56.7)	87 (33.9)	
Year						
2012	5358 (22.1)	355 (19.5)	169 (20.5)	112 (19.8)	57 (22.2)	.001
2013	4583 (18.9)	357 (19.6)	169 (20.5)	129 (22.8)	40 (15.6)	
2014	5839 (24.1)	579 (31.8)	85 (10.3)	44 (7.8)	41 (16.0)	
2015	4173 (17.2)	363 (19.9)	137 (16.6)	101 (17.8)	36 (14.0)	
2016	4315 (17.8)	168 (9.2)	263 (32.0)	180 (31.8)	83 (32.3)	
Age, y						
0–4	17 851 (73.6)	1124 (61.7)	484 (58.8)	314 (55.5)	170 (66.1)	.037
5–17	3407 (14.0)	374 (20.5)	207 (25.2)	153 (27.0)	54 (21.0)	
18–39	1770 (7.3)	214 (11.7)	84 (10.2)	64 (11.3)	20 (7.8)	
≥40	1240 (5.1)	110 (6.0)	48 (5.8)	35 (6.2)	13 (5.1)	
Sex						
Male	12 646 (52.1)	915 (50.2)	413 (50.2)	285 (50.4)	128 (49.8)	.884
Female	11 622 (47.9)	907 (49.8)	410 (49.8)	281 (49.6)	129 (50.2)	
Underlying medical conditions[a]						
Any	2159 (13.3)	81 (9.5)	48 (11.6)	28 (11.4)	20 (11.8)	.916
Multiple	239 (1.5)	10 (1.2)	9 (2.2)	4 (1.6)	5 (2.9)	.368
HIV infection	198 (1.2)	8 (0.9)	7 (1.7)	4 (1.6)	3 (1.8)	.593
New TB/prior TB	498 (3.1)	13 (1.5)	10 (2.4)	3 (1.2)	7 (4.1)	.059
Heart disease	241 (1.5)	6 (0.7)	6 (1.4)	3 (1.2)	3 (1.8)	.508
Liver disease	39 (0.2)	1 (0.1)	1 (0.2)	1 (0.4)	0 (0.0)	.446
Renal disease	33 (0.2)	1 (0.1)	2 (0.5)	1 (0.4)	1 (0.6)	.694
Diabetes	76 (0.5)	5 (0.6)	2 (0.5)	1 (0.4)	1 (0.6)	.699
Asthma	427 (2.6)	15 (1.8)	13 (3.1)	10 (4.1)	3 (1.8)	.277

Abbreviation: TB, tuberculosis.

[a]These data were not collected among the outpatients. Percentages were calculated among hospitalized patients.

[b]Chi-square test comparing influenza B cases that were genotyped with those that were not genotyped.

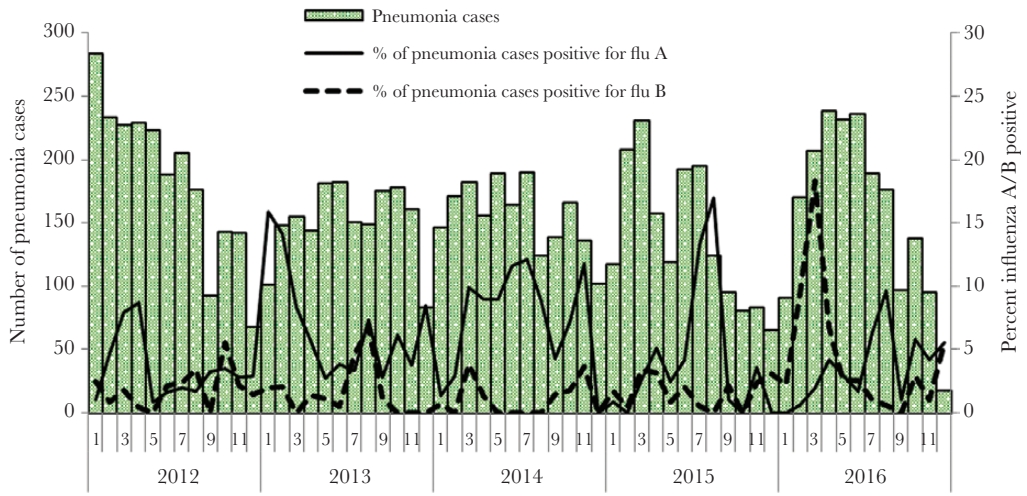

Figure 2. Monthly number of pneumonia cases and percentages associated with influenza A and B viruses among inpatients and outpatients enrolled from 11 surveillance sites in Kenya, 2012–2016. The months of April–September correspond to the Southern Hemisphere influenza season, and October–March (in the next year) correspond to the Northern Hemisphere season.

Table 2. Characteristics Associated With Influenza B Lineages Among Hospitalized and Outpatient Children Aged <5 Years who Tested Positive for Influenza B From 11 Surveillance Sites in Kenya, 2012–2016

	Inpatients			Outpatients		
	B/Victoria, No. (%)	B/Yamagata, No. (%)		B/Victoria, No. (%)	B/Yamagata, No. (%)	
Variable	n = 94	n = 77	*P* Value	n = 77	n = 66	*P* Value
Year						
2012	23 (24.5)	5 (6.5)	**<.001***	25 (32.5)	2 (3.0)	**<.001***
2013	2 (2.1)	34 (44.2)		8 (10.4)	30 (45.5)	
2014	0 (0.0)	5 (6.5)		1 (1.3)	15 (22.7)	
2015	2 (2.1)	26 (33.8)		0 (0.0)	17 (25.8)	
2016	67 (71.3)	7 (9.1)		43 (55.8)	2 (3.0)	
Demographics						
Age, y						
0–11 mo	31 (33.0)	21 (27.3)	.674	7 (9.1)	12 (18.2)	.276
12–23 mo	26 (27.7)	25 (32.5)		16 (20.8)	13 (19.7)	
24–59 mo	37 (39.4)	31 (40.3)		54 (70.1)	41 (62.1)	
Sex						
Male	58 (61.7)	48 (62.3)	.932	41 (53.2)	35 (53.0)	.979
Female	36 (38.3)	29 (37.7)		36 (46.8)	31 (47.0)	
Clinical signs and comorbidities						
Difficulty breathing	48 (51.1)	34 (44.2)	.368	1 (1.3)	3 (4.5)	.365*
Nasal flaring	41 (43.6)	14 (18.2)	**<.001**	0 (0.0)	2 (3.0)	.214*
Wheezing	12 (12.8)	8 (10.4)	.705	1 (1.3)	0 (0.0)	1.000*
Rhinorrhea	47 (50.0)	36 (46.8)	.882	66 (85.7)	52 (78.8)	.201
Chills	13 (13.8)	1 (1.3)	**.001***	0 (0.0)	1 (1.5)	1.000*
Grunting	10 (10.6)	10 (13.0)	.440	0 (0.0)	0 (0.0)	-
Unable to drink/breastfeed	7 (7.4)	6 (7.8)	.921	7 (9.1)	4 (6.1)	.550*
Chest-in-drawing	45 (47.9)	15 (19.5)	**<.001**	0 (0.0)	0 (0.0)	-
Hypoxia	13 (13.8)	1 (1.3)	**.018**	0 (0.0)	0 (0.0)	-
Laboratory-confirmed malaria						
Malaria negative	9 (9.6)	8 (10.4)	.247	28 (36.4)	17 (25.8)	.280
Malaria positive	3 (3.2)	7 (9.1)		8 (10.4)	9 (13.6)	
Unknown	82 (87.2)	62 (80.5)		41 (53.2)	40 (60.6)	
Had any underlying medical condition[a]	8 (8.5)	8 (10.4)	.675	-	-	
Weight-for-age						
Normal (Z-score >–2)	54 (57.4)	44 (57.1)	.696	35 (45.5)	37 (56.1)	.471*
Low (z-score >–3 and ≤–2)	11 (11.7)	11 (14.3)		8 (10.4)	4 (6.1)	
Very low (z-score ≤3)	12 (12.8)	7 (9.1)		2 (2.6)	2 (3.0)	
Unknown	17 (18.1)	15 (19.5)		32 (41.6)	23 (34.8)	
Clinical outcomes						
Pneumonia cases						
No pneumonia	34 (36.2)	43 (55.8)	**.010**	61 (79.2)	52 (78.8)	.909
Pneumonia	60 (63.8)	34 (44.2)		16 (20.8)	13 (19.7)	
Unknown	0 (0.0)	0 (0.0)		0 (0.0)	1 (1.5)	
Duration of illness (onset to admission/outpatient visit)						
<3 d	41 (43.6)	34 (44.2)	.777*	51 (66.2)	40 (60.6)	.538*
3–7 d	44 (46.8)	38 (49.4)		26 (33.8)	25 (37.9)	
≥8 d	9 (9.6)	5 (6.5)		0 (0.0)	1 (1.5)	
Median (IQR)	3.0 (2.0–6.0)	3.0 (1.0–4.0)	.282	2.0 (1.0–3.0)	2.0 (2.0–3.0)	.487
Duration of hospitalization						
<3 d	44 (46.8)	30 (39.0)	.452	-	-	
3–7 d	19 (20.2)	8 (10.4)		-	-	
≥8 d	6 (6.4)	19 (24.7)		-	-	
Median (IQR)	4.0 (2.0–7.0)	3.0 (2.0–6.0)	.068			
Died in hospital	6 (6.4)	0 (0.0)	**.042***	-	-	

Bold formatting indicates statistical significance at $P < .05$.

Abbreviation: IQR, interquartile range.

*Fisher exact test used instead of chi-square test.

[a]Chronic conditions: cardiac disease, liver disease, renal disease, diabetes, tuberculosis, HIV/AIDS, asthma, cancer, malnutrition, chronic neurological or neuromuscular disease.

days) compared with those who tested positive for B/Yamagata (3 [2–6] days), but the difference was not statistically significant (P = .062). There were no statistically significant differences in the clinical presentation among outpatient children aged <5 years by influenza B lineage (Table 2). There was no association between influenza B lineage and clinical outcomes among patients aged ≥5 years, either hospitalized or seen as outpatients (Supplementary Table 1).

Assessing the Match Between Influenza Lineage Types and Available TIV Vaccines

Influenza virus type B represented >40% of influenza viruses detected in 5/9 study seasons. Over the analysis period, the predominant B lineage matched the available TIV vaccines in 7/9 seasons, whereas there was a mismatch in 2/9 seasons (October 2012 to March 2013 and October 2015 to March 2016). During the October 2015 to March 2016 season, where 85% of all influenza cases tested were type B, and of those 95% were B/Victoria, the use of TIV might not have prevented about 95% of all the influenza B cases, assuming no cross-positivity. Among the 4 NH seasons assessed, 65% (208/320) of all influenza B cases were not covered by the available vaccine, whereas among the 5 SH seasons assessed, 8% (18/238) were not covered. Lineage co-circulation (>10% of both lineage types were detected) was noted in 3/9 seasons (April 2012–September 2012, October 2012–March 2013, and April 2016–September 2016) (Table 3).

Rates of Hospitalizations Associated With Influenza B by Lineage Type

Over the 4-year period, the overall mean annual rates of hospitalizations associated with B/Victoria and B/Yamagata among patients with SARI in Siaya County were 12 (95% CI, 6–21) and 10 (95% CI, 6–20) per 100 000 person-years, respectively (Supplementary Table 2). Rates were much higher among children aged <5 years, where the mean annual rates of SARI hospitalizations associated with influenza B/Victoria and B/Yamagata were 27 (95% CI, 9–76) and 41 (95% CI, 17–95) per 100 000 person-years, respectively (Figure 3; Supplementary Table 2). Overall, the annual rates of B/Victoria were highest in 2016 (27/100 000 person-years; 95% CI, 18–40/100 000 person-years) and lowest in 2014 (3/100 000 person-years; 95% CI, 1–9/100 000 person-years). For B/Yamagata, the overall annual rates were highest in 2015 (21/100 000 person-years; 95% CI, 14–33/100 000 person-years) and lowest in 2016 (3/100 000 person-years; 95% CI, 1–10/100 000 person-years) when B/Victoria was dominant (Figure 2; Supplementary Table 2).

Rates of Outpatient Visits Associated With Influenza B by Lineage Type

Overall, the mean annual rates of outpatient visits associated with B/Victoria and B/Yamagata in Siaya County were 117 (95% CI, 83–163) and 118 (95% CI, 85–165) per 100 000 person-years, respectively (Supplementary Table 3). As with hospitalizations, the rates of outpatient visits were higher among children aged <5 years compared with those aged ≥5 years; the estimated mean annual rate associated with influenza B/Victoria was 344/100 000 person-years (95% CI, 202–586/100 000 person-years), and it was 341/100 000 person-years (95% CI, 200–583/100 000 person-years) for B/Yamagata (Figure 4; Supplementary Table 3).

Ratio of Hospitalizations to Outpatient Visits by Influenza Virus Type

Over the 5-year study period, the mean annual rates of hospitalizations and outpatient visits associated with influenza virus A were 34/100 000 person-years (95% CI, 24–49/100 000 person-years) and 532/100 000 person-years (95% CI,

Table 3. Distribution of Influenza B/Victoria and B/Yamagata Lineage Types Circulating in Kenya Compared With Influenza Vaccine Hemisphere Composition by Year From 11 Surveillance Sites in Kenya, 2012–2016

Season	All Influenza Positive	Influenza B Positive	Influenza B Type	B/Victoria	B/Yamagata	TIV Influenza B Vaccine Component	Influenza B Cases not Covered by Available Vaccine[c]
		No. (%)	No.	No. (%)	No. (%)		%
Apr 2012–Sep 2012 (SH)	210	96 (45.7)	59	53 (89.8)	6 (10.2)[c]	B/Brisbane/60/2008 (B/Victoria)	10
Oct 2012–Mar 2013 (NH)	329	99 (30.1)	88	63 (71.6)	25 (28.4)	B/Wisconsin/1/2010 (B/Yamagata)[a]	72
Apr 2013–Sep 2013 (SH)	225	95 (42.2)	67	3 (4.5)	64 (95.5)	B/Wisconsin/1/2010 (B/Yamagata)	4
Oct 2013–Mar 2014 (NH)	220	52 (23.6)	26	0 (0.0)	26 (100.0)	B/Massachusetts/2/2012 (B/Yamagata)	0
Apr 2014–Sep 2014 (SH)	395	18 (4.6)	7	0 (0.0)	7 (100.0)	B/Massachusetts/2/2012 (B/Yamagata)	0
Oct 2014–Mar 2015 (NH)	184	75 (40.8)	57	4 (7.0)	53 (93.0)	B/Massachusetts/2/2012 (B/Yamagata)	7
Apr 2015–Sep 2015 (SH)	413	93 (22.5)	66	4 (6.1)	63 (95.5)	B/Phuket/3073/2013 (B/Yamagata)[b]	6
Oct 2015–Mar 2016 (NH)	210	179 (85.2)	149	141 (94.6)	9 (6.0)	B/Phuket/3073/2013 (B/Yamagata)[a]	95
Apr 2016–Sep 2016 (SH)	200	82 (41.0)	39	34 (87.2)	5 (12.8)	B/Brisbane/60/2008 (B/Victoria)	13

Abbreviations: NH, time when the Northern Hemisphere vaccine is available; SH, time when the Southern Hemisphere vaccine is available; TIV, trivalent influenza vaccine.

[a]Seasons with a mismatch of the influenza B component of the TIV vaccine.

[b]Had 1 patient with a co-infection of B/Victoria and B/Yamagata.

[c]Calculated as the crude percentage of influenza B cases that would not be potentially protected by the available TIV vaccine assuming no cross-protection.

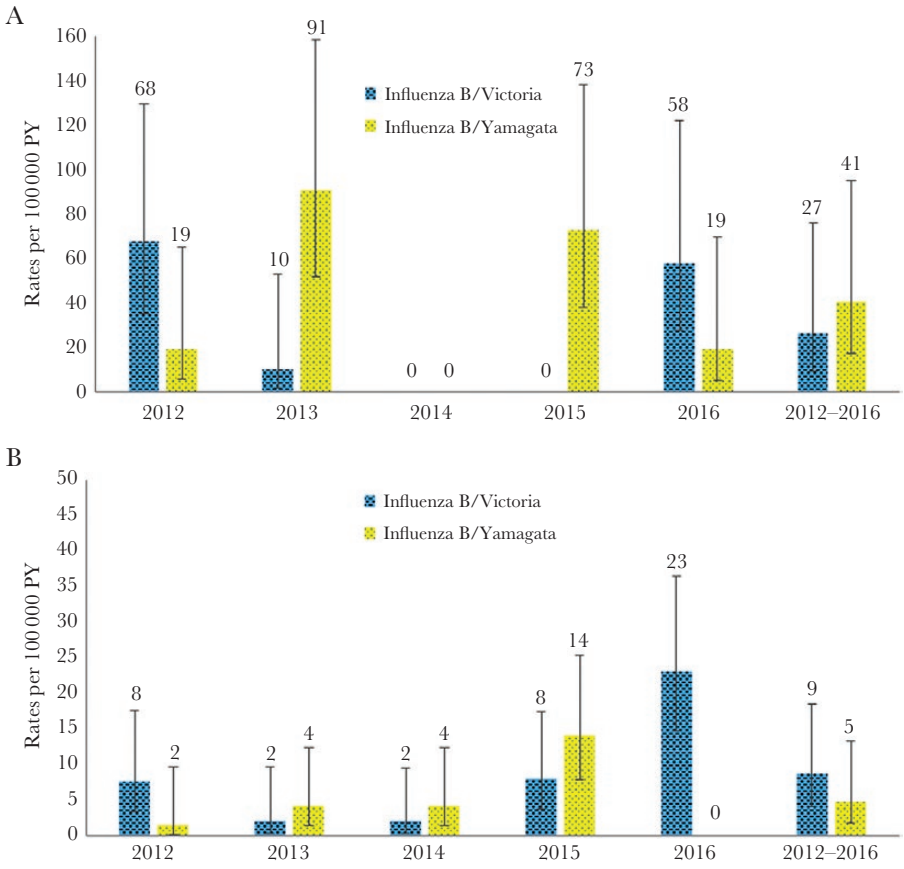

Figure 3. Rates of hospitalizations associated with influenza B/Victoria and B/Yamagata in Siaya over the period 2012–2016 among (A) children aged <5 years and (B) persons aged ≥5 years.

455–623/100 000 person-years), respectively, in Siaya county. For influenza type B, the mean annual rates for hospitalizations and outpatient visits were 21/100 000 person-years (95% CI, 13–33/100 000 person-years) and 191/100 000 person-years (95% CI, 147–249/100 000 person-years), respectively. The ratios of hospitalizations to outpatient visits were higher for influenza B in 4 of the 5 study-years other than in 2013, when it was highest for influenza A. However, these differences were not statistically significant. Overall, the mean ratios of hospitalizations to outpatient visits for influenza A and B were 0.06 (95% CI, 0.04–0.09) and 0.11 (95% CI, 0.07–0.18), respectively (Supplementary Table 4).

DISCUSSION

We found that influenza B virus infections in Kenya were associated with a substantial burden of medically attended disease among children aged <5 years. Among children aged <5 years, the B/Victoria lineage was associated with a higher frequency of pneumonia during hospitalization and with in-hospital death compared with B/Yamagata, suggesting more severe disease. We also found that the 2 lineages co-circulated in Kenya, and during 2/9 seasons there were mismatches with available TIV vaccines. Consistent with other studies [15–17, 31], our findings suggest that the use of QIV in Kenya could have a greater impact on reduction of disease burden when compared with TIV, especially among young children.

Although influenza A circulated in relatively higher proportions, influenza B co-circulated and was an important contributor to hospitalizations and outpatient visits in Kenya. Over the study period, influenza B contributed >40% of all the cases that were detected in 5 out of the 9 NH and SH seasons that were assessed. Influenza B was the dominant virus type in 2016. As previously reported, influenza B viruses can lead to severe disease and death [5, 6, 8]. Indeed, as shown by our study, the ratio of hospitalization rate to outpatient visit rate over the study period was 0.11 for influenza B compared with 0.06 for influenza A. This finding suggests that influenza B is no less important in causing severe illness and hospitalizations.

When the 2 influenza type B lineages were compared among children <5 years, our data suggested that B/Victoria was associated with more severe illness than B/Yamagata. This was indicated by the percentage of those who presented with pneumonia (64% vs 44%, including a longer duration of hospital stay) and the association with in-hospital mortality (6% of those with B/Victoria compared with none among those with

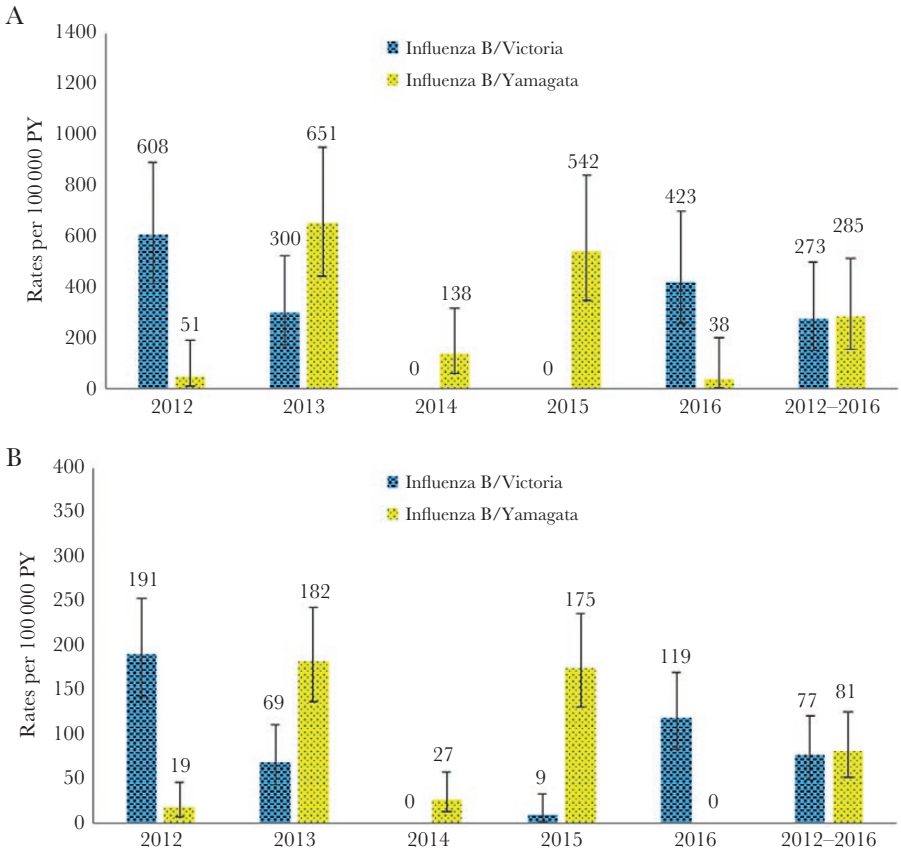

Figure 4. Rates of outpatient visits associated with influenza B/Victoria and B/Yamagata in Lwak over the period 2012–2016 among (A) children aged <5 years and (B) persons aged ≥5 years.

B/Yamagata). These findings are similar to those reported in Thailand, although data from Thailand have been reported for all ages combined [32]. Nonetheless, other studies using patients of all ages combined to compare clinical presentation by B lineage did not find significant clinical differences [33–35]. It is not clear whether an association with severe illness, as suggested in our study, is age-specific and/or affected by underlying characteristics of study population. Although our findings were statistically significant, further studies are warranted before concluding that disease severity differs by influenza B lineage.

An assessment of the distribution of the 2 lineage types, B/Victoria and B/Yamagata, over the 5-year period may suggest a pattern where one lineage type was gradually replaced by the other but re-emerged after 2 or 3 years. This pattern is similar to what has been shown elsewhere [33], and it may suggest that a specific lineage re-emerges and circulates in markedly higher levels after a sufficient pool of susceptible individuals has been accumulated in the population. The periods in between the dominance of particular lineage types also exhibited substantial levels of co-circulation of the 2 lineage types, as has been described elsewhere [2, 9, 33]. In Kenya, the 2 lineages co-circulated in 2013 and 2015, and this should be an important consideration for future prevention measures.

Although the influenza B virus lineage selected for inclusion in the TIV vaccines was well matched to the circulating lineage for most of the seasons included in our study, there were 2/9 seasons where there was an almost complete mismatch. Considering these scenarios together with the noted levels of co-circulation of the 2 lineage types, we see a potential benefit of using QIV compared with TIV in reducing the burden of influenza B virus infections in Kenya, as suggested by studies conducted elsewhere [15–17, 31]. However, it is important to note that the overall benefit of QIV over TIV may be dependent on several factors: the extent to which influenza B circulation dominates over A, how the mismatched lineage type dominates over the 1 included in the TIV vaccine, the level of cross-protection between the 2 influenza B lineages, prior infection, and vaccination history.

This study had several limitations. First, the assessment of clinical presentation associated with the 2 lineages may have been limited by the relatively small sample size, especially for outpatients and those aged ≥5 years. Due to sample size constraint, 95% CIs were wide, limiting the comparison of rates by lineage and patient type. Second, the use of different case definitions in recruiting respiratory cases at the various sites, especially for outpatients, where both ILI and ALRI case definitions

were used, may have affected our ability to identify differences in clinical presentation. Lastly, because of a relatively short period of analysis, we were not able to sufficiently discern the activity patterns of the 2 lineage types in Kenya.

CONCLUSIONS

Our findings suggest a substantial disease burden associated with medically attended influenza B in Kenya, particularly among young children aged <5 years. They highlight the potential benefit of using QIV compared with TIV when considering future policy recommendations.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Author contributions. G.O.E. and S.S.C. were involved in concept and design of the manuscript; B.O.N., F.O., and N.A.O. were involved in data collection; C.A. conducted the laboratory tests; G.O.E. analyzed the data and was the lead author in writing the manuscript; G.O.E., B.O.N., F.O., N.A.O., C.A., L.K.N., P.M., G.B., P.M.M., and E.H. were involved in interpretation of data and approved the final manuscript. S.S.C. provided critical supervision to the writing and analysis and interpretation of the data and approved the final version of the manuscript.

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