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.
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 setting (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
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 calcu-
lated 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, was 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, hospitali-
zation 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 hospital-
izations 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 sur-
veillance 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 ques-
tionnaires were administered and specimens collected.

RESULTS

Descriptive Analyses

From 2012 through 2016, 24 268 patients with ARI were en-
rolled at 11 surveillance sites in Kenya and tested for influenza
A and B viruses. Among these, 16 182 (67%) patients were hos-
pitalized 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 posi-
tive 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 influ-
enza A (5.7% vs 2.7%). In 2016, influenza activity was domi-
nated 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]
weeks) compared with B/Yamagata (2 [1–5] weeks; P = .042).

Emukule et al

OFID  •  4
### 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<sup>b</sup> |
|----------|--------------------------|-----------------------|----------------------|-----------------------|--------------------------|-------------------------------------------------------------|
|          | No. (%)                  | No. (%)               | No. (%)              | No. (%)               | No. (%)                  | PValue                                                       |
| 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 | 8,086 (33.3)            | 966 (53.0)            | 406 (49.6)           | 321 (56.7)            | 87 (33.9)                |                                                              |
| Year     |                          |                       |                      |                       |                          |                                                              |
| 2012     | 5,358 (22.1)             | 355 (19.5)            | 169 (20.5)           | 112 (19.8)            | 57 (22.2)                | .001                                                         |
| 2013     | 4,583 (18.9)             | 357 (19.6)            | 169 (20.5)           | 129 (22.8)            | 40 (15.6)                |                                                              |
| 2014     | 5,839 (24.1)             | 579 (31.8)            | 85 (10.3)            | 44 (7.8)              | 41 (16.0)                |                                                              |
| 2015     | 4,173 (17.2)             | 363 (19.9)            | 137 (16.6)           | 101 (17.8)            | 36 (14.0)                |                                                              |
| 2016     | 4,315 (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     | 3,407 (14.0)             | 374 (20.5)            | 207 (25.2)           | 153 (27.0)            | 54 (21.0)                |                                                              |
| 18–39    | 1,770 (7.3)              | 214 (11.7)            | 84 (10.2)            | 64 (11.3)             | 20 (7.8)                 |                                                              |
| ≥40      | 1,240 (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<sup>a</sup> |          |                       |                      |                       |                          |                                                              |
| Any      | 2,159 (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)                  | .693                                                         |
| 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.

<sup>a</sup>These data were not collected among the outpatients. Percentages were calculated among hospitalized patients.

<sup>b</sup>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

| Variable                          | Inpatients | Outpatients | PValue |
|-----------------------------------|------------|-------------|--------|
|                                   | B/Victoria, No. (%) | B/Yamagata, No. (%) | B/Victoria, No. (%) | B/Yamagata, No. (%) | PValue |
| Year                              | n = 94     | n = 77      |        | n = 77     | n = 66     |        |
| 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* | 8 (8.5)  | 8 (10.4)    | .675   | -          | -         |        |
| Weight-for-age                    |            |             |        |            |           |        |
| Normal (Z-score >–2)              | 54 (57.4)  | 44 (52.7)   | .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 (2.0–70) | 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.
*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) 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).

### 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 | Influenza B/Victoria | Influenza B/Yamagata | TIV Influenza B Vaccine Component | Influenza B Cases not Covered by Available Vaccine (%) |
|--------------|------------------------|----------------------|-----------------|----------------------|----------------------|----------------------------------|-----------------------------------------------------|
| Apr 2012–Sep 2012 (SH) | 210                    | 96 (45.7)            | 59              | 53 (89.8)            | 6 (10.2)             | B/Brisbane/002/2008 (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)     | 72                                                  |
| Apr 2013–Sep 2013 (SH) | 225                    | 95 (42.2)            | 67              | 4 (5.3)              | 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)              | 62 (93.5)           | B/Phuket/0073/2013 (B/Yamagata)     | 6                                                   |
| Oct 2015–Mar 2016 (NH) | 210                    | 179 (85.2)           | 149             | 141 (94.8)           | 9 (6.0)             | B/Phuket/0073/2013 (B/Yamagata)     | 95                                                  |
| Apr 2016–Sep 2016 (SH) | 200                    | 82 (41.0)            | 39              | 34 (87.2)            | 5 (12.8)            | B/Brisbane/002/2008 (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.

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

*Had 1 patient with a co-infection of B/Victoria and B/Yamagata.

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

The Burden of Influenza B in Kenya • OFID • 7
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
ofid • 9

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 are used. Third, the assessment of clinical presentation 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.
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.

**Acknowledgments**

The authors wish to thank the influenza surveillance officers at all the participating sites and the laboratory and data management staff at the Kenya Medical Research Institute (KEMRI), without whom this study would not have taken place. The authors also acknowledge the important role played by the Kenya Ministry of Health officials at the national level by Ms. Rosalia Kalani and the health care workers at the participating surveillance sites. Special acknowledgment to Dr. Marc-Alain Widdowson for reviewing the final draft of this manuscript.

**Financial support.** This study was supported by the US Centers for Disease Control and Prevention. The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

**Disclaimer.** The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

**Potential conflicts of interest.** All authors: no reported conflicts of interest.

**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 and analysis; 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., 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.

**References**

1. Dawood FS, Fiore A, Kamimoto L, et al; Emerging Infections Program Network. Burden of seasonal influenza hospitalization in children, United States, 2003 to 2008. J Pediatr 2010; 157:808–14.

2. Cowling BJ, Wu P, Lo JYC, et al. Population-based pediatric hospitalization burden of lineage-specific Influenza B in Hong Kong, 2004-2014. Clin Infect Dis 2017; 65:300–7.

3. Ahmed JA, Katz MA, Auko E, et al. Epidemiology of respiratory viral infections in two long-term refugee camps in Kenya, 2007-2010. BMC Infect Dis 2012; 12:7.

4. Cohen JM, Silva ML, Caini S, et al; IBGP Study Team. Striking similarities in the presentation and duration of illness of influenza A and B in the community: a study based on sentinel surveillance networks in France and Turkey, 2010-2012. PLoS One 2015; 10:e0139431.

5. Su S, Chaves SS, Perez A, et al. Comparing clinical characteristics between hospitalized adults with laboratory-confirmed influenza A and B virus infection. Clin Infect Dis 2014; 59:252–5.

6. Gutierrez Pizaraya A, Perez-Romero P, Alvarez R, et al. Unexpected severity of cases of influenza B infection in patients that required hospitalization during the first postpandemic wave. J Infect 2012; 65:423–30.

7. Paddock CD, Liu L, Denison AM, et al. Myocardial injury and bacterial pneumonia contribute to the pathogenesis of fatal influenza B virus infection. J Infect Dis 2012; 205:985–905.

8. Harvala H, Smith D, Salvaterra K, et al. Burden of influenza B virus infections in Scotland in 2012/13 and epidemiological investigations between 2000 and 2012. Euro Surveill 2014; 19.

9. Cai ni S, Huang QS, Ciblah MA, et al; Global Influenza B Study. Epidemiological and virological characteristics of influenza B: results of the Global Influenza B Study. Influenza Other Respir Viruses 2015; 9(Suppl 1):3–12.

10. Osi R, Colomba GME, Pojero F, et al. Trends of influenza B during the 2010-2016 seasons in 2 regions of North and South Italy: the impact of the vaccine mismatch on influenza immunisation strategy. Hum Vaccin Immunother 2018; 14:523–31.

11. Barr IG, Jelley LL. The coming era of quadrivalent human influenza vaccines: who will benefit? Drugs 2012; 72:2177–85.

12. Belshe RB. The need for quadrivalent vaccine against seasonal influenza. Vaccine 2010; 28(Suppl 4):D45–53.

13. Centers for Disease Control and Prevention. Prevention and control of seasonal influenza with vaccines. Recommendations of the Advisory Committee On Immunization Practices, 2013–24. MMWR Morb Mortal Wkly Rep 2013; 62(RR07):1–43.

14. Clements KM, Meier G, McGarry LJ, et al. Cost-effectiveness analysis of universal influenza vaccination with quadrivalent inactivated vaccine in the United States. Hum Vaccin Immunother 2014; 10:171–80.

15. de Boer PT, Crépé P, Pitman RJ, et al. Cost-effectiveness of quadrivalent versus trivalent influenza vaccine in the United States. Value Health 2016; 19:964–75.

16. Jamotte A, Clay E, Macabo R, et al. Public health impact and economic benefits of quadrivalent influenza vaccine in Latin America. Hum Vaccin Immunother 2017; 13:877–85.

17. Reed C, Meltzer MI, Finelli L, Fiore A. Public health impact of including two lineages of influenza B in a quadrivalent seasonal influenza vaccine. Vaccine 2012; 30:1993–8.

18. Hendriks I, Hutubessy RCW, Grohmann G, et al. Quadrivalent influenza vaccines in low and middle income countries: cost-effectiveness, affordability and availability. Vaccine 2018; 36:3993–7.

19. Dawa JA, Chaves SS, Nyawanda B, et al. National burden of hospitalized and non-hospitalized influenza-associated severe acute respiratory illness in Kenya, 2012-2014. Influenza Other Respir Viruses 2018; 12:30–7.

20. Fuller JA, Summers A, Katz MA, et al. Estimation of the national disease burden of influenza-associated severe acute respiratory illness in Kenya and Guatemala: a novel methodology. PLoS One 2013; 8:e56882.

21. Emukule GO, Paget J, van der Velden K, Mott JA. Influenza-associated disease burden in Kenya: a systematic review of literature. PLoS One 2015; 10:e0138708.

22. Emukule GO, Mott JA, Spreeuwenberg P, et al. Influenza activity in Kenya, 2007-2010. Pediatr Infect Dis J 2012; 30:e513–20.

23. Emukule GO, Khagayi S, McMorrow ML, et al. The burden of influenza and RSV pneumonia in two long-term refugee camps in Kenya, 2007-2010. Pediatr Infect Dis J 2012; 31:e553–60.

24. Emukule GO, Mott JA, Spreeuwenberg P, et al. Influenza activity in Kenya, 2007-2010. Pediatr Infect Dis J 2012; 31:e553–60.

25. Feikin DR, Ngjema MR, Buggo G, et al. 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. Pediatr Infect Dis J 2013; 32:e14–9.

26. Katz MA, Lebo E, Emukule G, et al. Epidemiology, seasonality, and burden of influenza and influenza-like illness in urban and rural Kenya, 2007–2010. J Infect Dis 2012; 206(Suppl 1):S53–60.

27. Katz MA, Muthoka P, Emukule GO, et al. Results from the first six years of national sentinel surveillance for influenza in Kenya, July 2007-June 2013. PLoS One 2014; 9:e105543.

28. World Health Organization. WHO child growth standards: methods and development. Available at: http://www.who.int/childgrowth/standards/technical_report/en/. Accessed 18 April 2018.

29. World Health Organization. WHO recommendations on the composition of influenza virus vaccines. Available at: http://www.who.int/influenza/vaccines/ virus/recommendations/en/. Accessed 5 June 2018.

30. Ulm K. A simple method to calculate the confidence interval of a standardized mortality ratio (SMR). Am J Epidemiol 1990; 131:373–5.

31. Jamotte A, Chong CE, Manton A, et al. Impact of quadrivalent influenza vaccine on public health and influenza-related costs in Australia. BMC Public Health 2016; 16:630.
32. Horthongkham N, Athipanyasilp N, Pattama A, et al. Epidemiological, clinical and virological characteristics of influenza B virus from patients at the hospital tertiary care units in Bangkok during 2011-2014. PLoS One 2016; 11:e0158244.
33. Seleka M, Treurnicht FK, Tempia S, et al. Epidemiology of influenza B/Yamagata and B/Victoria lineages in South Africa, 2005-2014. PLoS One 2017; 12:e0177655.
34. Sočan M, Prosenc K, Ulakar V, Berginc N. A comparison of the demographic and clinical characteristics of laboratory-confirmed influenza B Yamagata and Victoria lineage infection. J Clin Virol 2014; 61:156–60.
35. Tan Y, Guan W, Lam TT, et al. Differing epidemiological dynamics of influenza B virus lineages in Guangzhou, southern China, 2009-2010. J Virol 2013; 87:12447–56.