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# Which influenza vaccine formulation should be used in Kenya? A comparison of influenza isolates from Kenya to vaccine strains, 2007–2013

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ABSTRACT

*Introduction:* Every year the World Health Organization (WHO) recommends which influenza virus strains should be included in a northern hemisphere (NH) and a southern hemisphere (SH) influenza vaccine. To determine the best vaccine formulation for Kenya, we compared influenza viruses collected in Kenya from April 2007 to May 2013 to WHO vaccine strains.

*Methods:* We collected nasopharyngeal and oropharyngeal (NP/OP) specimens from patients with respiratory illness, tested them for influenza, isolated influenza viruses from a proportion of positive specimens, tested the isolates for antigenic relatedness to vaccine strains, and determined the percentage match between circulating viruses and SH or NH influenza vaccine composition and schedule.

*Results:* During the six years, 7.336 of the 60,072 (12.2%) NP/OP specimens we collected were positive for influenza: 30,167 specimens were collected during the SH seasons and 3717 (12.3%) were positive for influenza; 2903 (78.1%) influenza A, 902 (24.2%) influenza B, and 88 (2.4%) influenza A and B positive specimens. We collected 30,131 specimens during the NH seasons and 3978 (13.2%) were positive for influenza; 3181 (80.0%) influenza A, 851 (21.4%) influenza B, and 54 (1.4%) influenza A and B positive specimens. Overall, 362/460 (78.7%) isolates from the SH seasons and 316/338 (93.5%) isolates from the NH seasons were matched to the SH and the NH vaccine strains, respectively ($p < 0.001$). Overall, 53.6% and 46.4% SH and NH vaccines, respectively, matched circulating strains in terms of vaccine strains and timing.

*Conclusion:* In six years of surveillance in Kenya, influenza circulated at nearly equal levels during the SH and the NH influenza seasons. Circulating viruses were matched to vaccine strains. The vaccine match decreased when both vaccine strains and timing were taken into consideration. Either vaccine formulation could be suitable for use in Kenya but the optimal timing for influenza vaccination needs to be determined.



## 1. Introduction

Influenza is a viral infection that circulates worldwide, and causes seasonal epidemics and pandemics [1,2]. In 2008, an estimated 90 million cases of influenza occurred globally, including 28,000–111,500 deaths in children <5 years old; 99% of the deaths occurred in developing countries [3]. In Africa, recent surveillance data have demonstrated significant morbidity and mortality associated with influenza [4–7], and in Kenya the annual burden of hospitalized influenza has been shown to be two to five times higher than estimates reported in the United States [8].

Vaccines provide the best protection against influenza viruses [9,10]. Because influenza viruses constantly change, the Global Influenza Surveillance and Response System and the six World Health Organization (WHO) influenza collaborating centers

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continuously analyze the antigenic and genetic characteristics of the circulating influenza viruses worldwide. Based on these analyses, the WHO makes recommendations on the influenza strains to be used in two vaccine formulations each year; the southern hemisphere (SH) recommendations are made in September to inform production and distribution the following April, while the northern hemisphere (NH) recommendations are made in February for vaccine production and distribution beginning in September [11,12]. Until 2014, each vaccine formulation was trivalent, containing one influenza A/H1N1, one A/H3N2, and one influenza B strain. From 2010 to present, the A/H1N1 vaccine strain in both formulations has been a 2009 pandemic influenza A/H1N1 (A/H1N1pdm09) virus.

For influenza vaccination programs to be effective, two main conditions must be met. First, the vaccine must contain antigens that are matched to the majority of the viruses circulating following vaccination. Second, vaccines must be administered at the right time – early enough to allow for antibodies to develop before seasonal influenza activity begins, but not too early so that immunity wanes before influenza activity peaks [13]. Vaccination with inactivated trivalent influenza vaccine produces protective influenza antibodies for up to nine or twelve months in most patients [14,15]. In addition, protection against viruses that are antigenically similar to those in the vaccine has been shown to last for six to eight months and longer, particularly in non-elderly populations [10]. In temperate regions, vaccination campaigns typically begin slightly before the beginning of the influenza season, which occurs during winter months, and rarely exceeds five to six months. In tropical climates, however, influenza seasonality is much less discrete and influenza often circulates year-round [7,16–18]. In these settings, the optimal formulation and timing of vaccination is much less clear.

Kenya, a country with a population of 38.6 million people in 2009 [19] lies between 5° N and 5° S of the equator and has a tropical climate. Influenza infections are a significant cause of respiratory illness [20]. In four out of six years of recent surveillance (2007–2013), influenza circulated year-round with slight peaks from July to November [21] but less than 30,000 doses of influenza vaccine are distributed annually [5]. Influenza vaccination is not included in the national immunizations program. However, in 2013 the Kenya Ministry of Health released its first influenza immunization guidelines, including suggested priority groups for influenza vaccination [22], which include children less than one year, persons 65 years and older, adults and children six months and older with chronic conditions, health workers with frequent contact with high risk persons, and house-hold contacts of high-risk persons.

In order to inform future decisions about the best vaccine formulation and the optimal timing of influenza vaccination in Kenya, we compared the influenza viruses circulating in Kenya from 2007 to 2013 to the viruses in the reference strains in WHO-recommended vaccines for the southern and northern hemisphere. We also quantified the effectiveness of the influenza vaccination strategy considering the SH and NH vaccine composition and timing using a method similar to that applied by de Mello et al., [18]. Briefly, effectiveness was defined as the proportion of matches between strains present in the vaccine each year and strains circulating during that epidemiological season. We conducted the analysis using a nine-month and 12-month period of presumptive vaccine-induced protection. Vaccination in the SH usually begins in April while vaccination in the NH begins in October; thus the period of potential nine-month vaccine-induced protection was defined as May to January for the SH vaccination schedule and November to July for the NH schedule, while the 12-month potential protective period was taken to be May to April and November to October for the SH and NH vaccines, respectively.

## 2. Materials and methods

The Kenya Ministry of Health and the United States Centers for Disease Control and Prevention-Kenya (CDC-Kenya) carried out influenza sentinel surveillance from 2006 to 2012 in 10 healthcare facilities, including a national referral hospital, seven provincial general hospitals, and two refugee camp hospitals (Fig. 1). The sites were reduced to seven in 2012. In addition, beginning in 2005, the Kenya Medical Research Institute (KEMRI) in collaboration with CDC-Kenya carried out population-based influenza surveillance in two sites; one urban site (Kibera) in Nairobi and one rural site (Lwak) in western Kenya [23]. At all sites, we conducted surveillance for influenza-like illness (ILI) and severe acute respiratory illness (SARI) in patients of all ages, as previously described [5,21,23].

For all eligible patients, we collected nasopharyngeal (NP) and oropharyngeal (OP) specimens, which were placed in a cryovial containing 1 mL of viral transport media and shipped to the KEMRI/CDC laboratory in Nairobi for testing [24,25]. We tested the specimens for influenza A and B by real time reverse transcription polymerase chain reaction (rRT-PCR) as previously described [24]. Briefly, one step rRT-PCR was carried out using the AgPath-ID™ One-Step RT-PCR kit (Applied Biosystems, Foster City, CA, USA). Following a reverse transcription step, a 45 cycle PCR reaction was run and fluorescence read at the annealing/extension step. Appropriate negative and positive control specimens were run alongside each reaction. The results were recorded as cyclic threshold (CT) values. When all controls met the stated requirements, any influenza A and B CT value < 40 was recorded as positive. Specimens with a CT ≥ 40 or no CT value were recorded as negative. Beginning in mid-2008 all specimens positive for influenza A were sub-typed for H1, H3, H5, and (beginning in May 2009) A/H1N1pdm09 using rRT-PCR. A subset of specimens collected earlier than this were also retrospectively subtyped.

Previous work in our laboratory had indicated that influenza virus isolation was rarely successful for samples with high CT values [26]; thus, virus isolation was attempted only on samples with CT values < 35. On a monthly basis, we attempted to isolate influenza viruses from a geographically representative subset of influenza-positive specimens, as previously described [24]. We sent isolates to the WHO Collaborating Center at the United States Centers for Disease Control and Prevention (Atlanta, GA, USA) for antigenic characterization. We compared the Kenyan isolates to reference (vaccine) strains, using the hemagglutination inhibition (HI) assay [27,28]. We considered isolates collected and tested during and after July 2008 to be antigenically matched to a reference strain in the WHO-recommended vaccine if its HI titer was equal to or within an eight-fold difference from the reference strain [29]. For isolates collected before July 2008, the HI titer cut off was equal to or within four-fold difference from the reference strain. These different approaches reflect the relevant testing guidelines in use during these two periods [27,28].

Because protective antibodies have been demonstrated in vaccinated people for six to eight months [10], nine months [15] and 12 months [14] following influenza vaccination, we conducted our analysis using two different presumptive vaccine protection periods; six months and nine months. On the six-month analysis, we compared isolates from specimens collected from May to October (SH season) to the SH vaccine strains and those collected from October to March (NH season) to NH vaccine strains. We chose these time periods based on reported peak seasonal influenza activity in SH and NH countries [18]. In SH countries, including South Africa, Australia, Argentina, Chile, Uruguay and Paraguay, peak influenza activity is from May to October [30–35]. In NH countries, including the United States and Canada, peak influenza activity is from October to March [36,37] and November to April