

Incidence and Seasonality of Influenza-Like Illnesses among Pregnant Women in Blantyre, Malawi

Titus H. Divala,¹ Linda Kalilani-Phiri,² Patricia Mawindo,¹ Oswald Nyirenda,¹
Atupele Kapito-Tembo,³ and Miriam K. Laufer^{4*}

¹Blantyre Malaria Project, University of Malawi College of Medicine, Blantyre, Malawi; ²Department of Community Health, University of Malawi College of Medicine, Blantyre, Malawi; ³Malaria Alert Centre, University of Malawi College of Medicine, Blantyre, Malawi; ⁴Institute for Global Health, University of Maryland School of Medicine, Baltimore, Maryland

Abstract. Pregnant women with influenza infection are at increased risk of developing complications compared with other adults. Information about burden of influenza in pregnant women in Africa is limited. To determine incidence and seasonality of influenza-like illness (ILI) in pregnant women in Blantyre, Malawi, we recruited a cohort of 450 pregnant women and conducted surveillance for ILI and malaria infection. We recorded gestational age and birthweight. We accrued 157 person-years of observation (PYO) and detected 37 episodes of ILI (24/100 PYO) and 83 episodes of malaria infection (including all new episodes of parasitemia) (53/100 PYO). ILI was the most common cause of fever, but was not associated with adverse pregnancy outcomes. ILI incidence peaked during the hot dry season. These results indicate that ILI is a significant burden among Malawian pregnant women and it is somewhat seasonal. Studies with molecular diagnostics are needed to establish influenza-specific burden and the potential role of vaccination.

Seasonal influenza carries a large burden of morbidity and mortality throughout the world. Globally, the estimated annual attack rate in adults is 10% and results in 5 million cases of severe illnesses and 500,000 deaths.¹ Pregnant women are at significantly higher risk of severe influenza illness, its complications, and mortality when compared with nonpregnant adults.² This susceptibility is attributed to the maternal cardiac, respiratory, and hormonal physiological changes that occur to accommodate fetal development.^{2,3} Influenza infection has also been associated with miscarriage, stillbirth, preterm birth, low birth weight, and neonatal death.^{4,5} These are thought to be due to direct action of the influenza virus on the placenta and the fetus.⁶

Although respiratory infections are the second leading cause of death in sub-Saharan Africa,⁷ the etiology and burden of these infections is poorly understood. Studies within Africa have identified influenza as a leading cause of febrile morbidity.^{8,9} Specifically in Malawi, respiratory infections are the second leading cause of mortality,⁷ and 14% of febrile hospital presentations with respiratory complaints have been attributed to influenza.¹⁰ Descriptions of the burden of influenza in Africa that focus on pregnant women are rare.

Influenza is a disease that is at least partially preventable by vaccination,¹¹ but vaccine effectiveness is maximized by timing of administration to protect during the influenza season.¹² Vaccination is most effective if it precedes onset of the influenza season.¹³ Although influenza seasonality is well documented in western countries, data are limited for tropical southern African countries.^{14,15}

To describe the incidence and seasonality of influenza-like illness (ILI) and its impact on pregnancy outcomes in Malawi, we analyzed data from an observational cohort of pregnant women in Blantyre. We also took advantage of intensive active and passive malaria case detection in this cohort to examine the epidemiology of ILI and compare it to malaria

infection, another common cause of illness with important health impact for mothers and newborns in the region.

We used data collected in a prospective cohort study of malaria during pregnancy,¹⁶ conducted at Ndirande Health center in Blantyre, Malawi. We recruited human immunodeficiency virus (HIV)–negative women who were 1) at least 15 years of age, 2) in their first or second pregnancy, and 3) less than 28 weeks gestation. Participants reported to the research clinic every 4 weeks and whenever sick. At each visit, we recorded history of any illness, conducted physical examination, and performed light microscopy for malaria using blood films prepared from a finger-prick blood specimen. Upon delivery, we weighed and examined their infants. The gestational age at birth was determined based on last menstrual period or fundal height and Ballard examination. The study protocol was reviewed and approved by the University of Malawi College of Medicine Research and Ethics Committee and the University of Maryland Institutional Review Board. Details of this study were described previously.¹⁶

We defined ILI as acute onset of measured ($\geq 37.5^{\circ}\text{C}$) or reported fever, and either cough or sore throat, as classified by the European Centers for Disease Control and Prevention's case definition.¹⁷ We defined malaria infection as detection of *Plasmodium* parasites on thick smear by light microscopy regardless of the participant's clinical symptoms. We defined poor pregnancy outcomes using World Health Organization (WHO) standard definitions as follows: low birth weight (birth weight less than 2500 g), intrauterine growth restriction (birth weight for gestational age < -2.0 Z-score on WHO growth curves), and preterm delivery (less than 37 weeks gestation).

Data analysis was performed using STATA version 12.0 (Stata Corp., College Station, TX). The time under observation began at enrollment and ended at delivery or the last study visit. Individuals were considered continuously at risk of developing outcomes while under surveillance. New episodes of malaria infection were defined as a positive blood smear at least 2 weeks from the previous treatment, and new episodes of ILI were defined as symptoms that occurred after resolution of previous symptoms. New episodes were included in incidence calculations. Proportions were compared using

*Address correspondence to Miriam K. Laufer, Institute for Global Health, University of Maryland School of Medicine, 685 W. Baltimore St., HSF-1, Room 480, Baltimore, MD 21201. E-mail: mlauffer@medicine.umaryland.edu

TABLE 1
Baseline characteristics of the 450 enrolled pregnant women in Blantyre, Malawi

| Characteristic | Experienced at least one ILI episode (N = 34) | Experienced no ILI (N = 413) | P value |
|--|---|------------------------------|---------|
| Mean age (SD), years | 19.8 (0.4) | 20.2 (0.2) | 0.25 |
| Attended some secondary education (%) | 25 (73.5%) | 306 (68.0%) | 0.51 |
| Slept under a bed net the previous night (%) | 12 (35.3%) | 210 (51.1%) | 0.08 |
| Primigravida (%) | 22 (64.7%) | 260 (63.0%) | 0.84 |

ILI = influenza-like illness; SD = standard deviation.

Fisher's exact test. Means were compared using Student's *t* test.

We enrolled 450 women from June 2009 to June 2010, accrued 157 person-years of observation, and detected 37 episodes of ILI. Women who developed at least one episode of ILI were similar to those who did not, with respect to age, gravidity, and bed net usage (Table 1). We were able to assess pregnancy outcomes for 71% (320/450) of the participants. Losses to follow-up were predominantly due to migration out of the study area and withdrawal of consent due to pressure from an influential family member.

The incidence rates of ILI and malaria infection in this population were 24 and 53 per 100 person-years, respectively (Table 2). We detected 91 episodes of fever representing incidence rate of 58 per 100 person-years. The most common cause of fever was ILI, which was associated with 41% (37/91) of the febrile episodes; these included 6% (5/91) with both ILI and malaria infection. Malaria diagnosis occurred in 14% (13/91) of febrile episodes and the rest were due to other infections including gastroenteritis, urinary tract infections, abscesses, and pelvic infections.

ILI showed a consistent seasonal variation. Over the 3-year period, no cases of ILI were documented in January–February. The incidence density was highest in June–December peaking in September–October, corresponding with the hot, dry season. This is in sharp contrast to malaria infection, diagnosed most frequently in the rainy season (Figure 1).

The mean birth weight was 2.8 kg (95% confidence interval [CI] = 2.8–2.9) and the estimated gestational age at delivery was 38.6 weeks (95% CI = 38.2–38.9). Fifty (15.1%) infants were born preterm, 58 (17.9%) were low birth weight and 43 (13.3%) were small for gestational age. Among participants who had at least one episode of ILI compared with those who did not experience any ILI, there were no significant differences in the prevalence of preterm delivery, intrauterine growth restriction, or low birth weight.

To our knowledge, this is the first study characterizing ILI among pregnant women in a malaria-endemic setting in

southern Africa and provides further evidence that the burden of ILI during pregnancy is high throughout the world.¹⁸ In Malawi, ILI is a common cause of health facility visits during pregnancy and represents a heavy burden on pregnant women's health and health-care resources. The incidence of ILI in this cohort of pregnant women was 3-fold higher than the rate of acute respiratory infection documented in Kenya among adults.¹⁹

One unique feature of our study lies in the concurrent malaria surveillance that allowed examination of ILI in the context of malaria infection and other potential etiologies of fever. Our results suggest that ILI and malaria coinfection is possible but it is not common. In clinical practice, the presence of ILI symptoms is unlikely to mask acute malaria infection, especially in a setting where women were receiving standard malaria prevention measures.

We have demonstrated that ILI incidence follows a broad seasonal pattern, falling somewhere between temperate and tropical seasonality patterns.¹⁴ This is consistent with the geographical location of Malawi lying almost midway between the equator and the tropic of Capricorn. An alternative explanation to this pattern could be that ILI due to respiratory pathogens other than influenza diluted more specific seasonality of influenza infection. Further studies with molecular diagnostics will more precisely define the seasonal pattern.

Our study did not find any association between antenatal ILI and adverse pregnancy outcomes. Although this is consistent with some previous studies,²⁰ it may also be explained by the limited specificity of our ILI case definition. Many noninfluenza illnesses that meet the case definition of ILI may not have any impact on pregnancy outcomes, and may have limited the study's power to demonstrate this association. In addition, unobserved pregnancy time due to late enrollment (24 weeks gestation on average) may have further limited our study's ability to capture all ILI cases during pregnancy. The burden of ILI may have been underestimated as symptoms may have been mild and self-limited and may not have prompted health-seeking behavior. If cases were not identified, this may have prevented us from detecting the impact of ILI on birth outcomes.

Malawi has a strong platform for preventive services in pregnancy, including bed nets, malaria preventive therapy, prevention of mother to child transmission of HIV, and tetanus vaccination. Experience with these, along with the growing global efforts to make immunizations more accessible, make Malawi ideally suited for the introduction of a maternal influenza vaccination program. Our results of high rates of ILI in pregnant women provide the evidence for future studies powered to define the specific contribution of influenza and other respiratory pathogens in Malawi to maternal and infant health. These data may support an important role of influenza vaccination to protect women and their newborns in Malawi and the region.

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Authors' addresses: Titus H. Divala, Patricia Mawindo, and Oswald Nyirenda, Blantyre Malaria Project, University of Malawi College of Medicine, Blantyre, Malawi, E-mails: tdivala@gmail.com, patmawindo@gmail.com, and omnyirenda@gmail.com. Linda Kalilani-Phiri, Department of Public Health, University of Malawi College of Medicine, Blantyre, Malawi, E-mail: lkalilani@hotmail.com. Atupele Kapito-Tembo, Malaria Alert Centre, University of Malawi College of

TABLE 2

| Incidence rate of ILI, malaria and ILI, and malaria coinfection | | |
|---|--------|--|
| Diagnosis | Events | Incidence rate per 100 person years (95% CI) |
| ILI | 37 | 24 (16.6–32.1) |
| Malaria infection* | 83 | 53 (42.1–65.5) |
| ILI and malaria† | 5 | 3 (1.0–7.4) |

CI = confidence interval; ILI = influenza-like illness.

*Malaria infection = detection of *Plasmodium* parasites on thick smear by light microscopy.

†ILI and malaria = cases meeting criteria for both malaria and ILI.

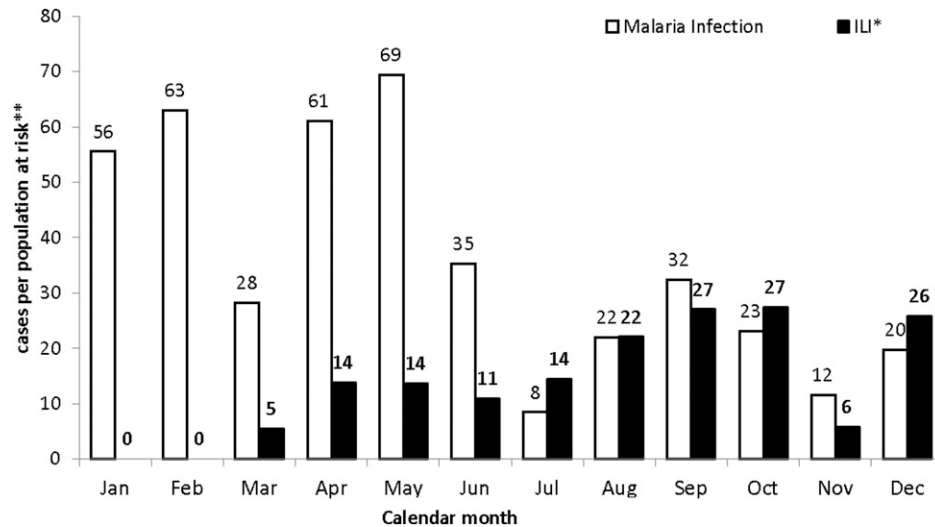


FIGURE 1. Monthly incidence density of ILI and malaria during pregnancy follow-up. * ILI = influenza-like illness; ** number of cases recorded per 1,000 person months in each calendar month.

Medicine, Blantyre, Malawi, E-mail: atupelekapito@gmail.com. Miriam K. Laufer, Division of Malaria Research, Institute for Global Health, University of Maryland School of Medicine, Baltimore, MD, E-mail: mlauger@medicine.umaryland.edu.

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