

Impact of a Point-of-Care Rapid Influenza Test on Antibiotic Prescribing Patterns in

Southern Sri Lanka

by

L. Gayani Tillekeratne

Duke Global Health Institute

Date: _____

Approved:

Christopher W. Woods, Supervisor

Nathan M. Thielman

Truls Ostbye

Champica K. Bodinayake

Megan E. Reller

Thesis submitted in partial fulfillment of
the requirements for the degree of
Master of Science in the Duke Global Health Institute in the Graduate School of Duke
University

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ABSTRACT

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Abstract

Background: Acute febrile respiratory illnesses, including influenza, account for a large proportion of ambulatory care visits worldwide. In the developed world, these encounters commonly result in unwarranted antibiotic prescriptions; data from more resource-limited settings are lacking. The purpose of this study was to describe the epidemiology of influenza among outpatients in southern Sri Lanka and to determine if access to rapid influenza test results was associated with decreased antibiotic prescriptions.

Methods: In this pretest- posttest study, consecutive patients presenting from March 2013- April 2014 to the Outpatient Department of the largest tertiary care hospital in southern Sri Lanka were surveyed for influenza-like illness (ILI). Patients meeting World Health Organization criteria for ILI-- acute onset of fever $\geq 38.0^{\circ}\text{C}$ and cough in the prior 7 days— were enrolled. Consenting patients were administered a structured questionnaire, physical examination, and nasal/nasopharyngeal sampling. Rapid influenza A/B testing (Veritor System, Becton Dickinson) was performed on all patients, but test results were only released to patients and clinicians during the second phase of the study (December 2013- April 2014).

Results: We enrolled 397 patients with ILI, with 217 (54.7%) adults ≥ 12 years and 188 (47.4%) females. A total of 179 (45.8%) tested positive for influenza by rapid testing,

with April- July 2013 and September- November 2013 being the periods with the highest proportion of ILI due to influenza. A total of 310 (78.1%) patients with ILI received a prescription for an antibiotic from their outpatient provider. The proportion of patients prescribed antibiotics decreased from 81.4% in the first phase to 66.3% in the second phase ($p=.005$); among rapid influenza-positive patients, antibiotic prescriptions decreased from 83.7% in the first phase to 56.3% in the second phase ($p=.001$). On multivariable analysis, having a positive rapid influenza test available to clinicians was associated with decreased antibiotic use (OR 0.20, 95% CI 0.05- 0.82).

Conclusions: Influenza virus accounted for almost 50% of acute febrile respiratory illness in this study, but most patients were prescribed antibiotics. Providing rapid influenza test results to clinicians was associated with fewer antibiotic prescriptions, but overall prescription of antibiotics remained high. In this developing country setting, a multi-faceted approach that includes improved access to rapid diagnostic tests may help decrease antibiotic use and combat antimicrobial resistance.

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1. Background

1.1 Global burden and seasonality of influenza

Acute febrile respiratory illnesses account for a large burden of morbidity and mortality worldwide, especially in developing settings where the majority of deaths occur.^{1,2} Viral pathogens such as influenza virus, respiratory syncytial virus, parainfluenza virus, adenovirus, and rhinovirus are responsible for most respiratory infections, although secondary bacterial infections are estimated to occur in up to 10-50% of these patients.³ Influenza virus, in particular, has the potential to cause pandemics and accounts for significant morbidity, lost productivity, and healthcare utilization each year.⁴

Data from higher-income countries indicate that seasonal influenza infections occur in 10-20% of the world's population annually, with 3-5 million cases of severe

¹ Kono, J., Jonduo, M. H., Omena, M., Siba, P. M., & Horwood, P. F. (2014). Viruses Associated With Influenza-Like-Illnesses in Papua New Guinea, 2010. *Journal of Medical Virology*, 86, 899–904.

² Lozano, R., Naghavi, M., Foreman, K., Lim, S., Shibuya, K., Aboyans, V., ... Ahn, S. Y. (2012). Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*, 380(9859), 2095–128.

³ Peltola, V., & Ruuskanen, O. (2008). Editorial commentary: Respiratory viral infections in developing countries: common, severe, and unrecognized. *Clinical Infectious Diseases*, 46(1), 58–60.

⁴ Peasah, S. K., Azziz-Baumgartner, E., Breese, J., Meltzer, M. I., & Widdowson, M.-A. (2013). Influenza cost and cost-effectiveness studies globally--a review. *Vaccine*, 31(46), 5339–48.

illness and 250,000- 500,000 deaths.⁵ While the virus causes a large disease burden in all parts of the globe, a recent meta-analysis suggested a higher case fatality rate in children from developing countries, with 2.9% deaths compared to 0.2% in more developed settings.⁶ This difference in mortality may be attributable to higher rates of vaccination in developed settings, in addition to better diagnostics and supportive care. In higher-income settings, influenza patterns are well characterized and coordinated public health efforts allow risk communication messages and timed mass vaccination based on influenza activity. Data from the 2012- 2013 influenza season in the United States showed that vaccination resulted in a 17% reduction in severe disease, with an associated decrease in hospitalizations and medical visits.⁷

Influenza seasonality in temperate, higher-income countries typically coincides with the winter months, and is thought to be secondary to factors including virus survival, host susceptibility, and efficiency of transmission.⁸ In lower-income settings in

⁵ Peasah, S. K., Azziz-Baumgartner, E., Breese, J., Meltzer, M. I., & Widdowson, M.-A. (2013). Influenza cost and cost-effectiveness studies globally--a review. *Vaccine*, 31(46), 5339-48.

⁶ Nair, H., Brooks, W. A., Katz, M., Roca, A., Berkley, J. a, Madhi, S. a, ... Campbell, H. (2011). Global burden of respiratory infections due to seasonal influenza in young children: a systematic review and meta-analysis. *Lancet*, 378(9807), 1917-30.

⁷ Centers for Disease Control and Prevention. (2013a). Estimated influenza illnesses and hospitalizations averted by influenza vaccination-- United States, 2012- 13 influenza season. *MMWR*, 62(49), 993-6.

⁸ Willem, L., Van Kerckhove, K., Chao, D. L., Hens, N., & Beutels, P. (2012). A nice day for an infection? Weather conditions and social contact patterns relevant to influenza transmission. *PloS one*, 7(11), e48695.

tropical and subtropical settings, the patterns of influenza activity are poorly characterized due to lack of surveillance and laboratory capacity. An analysis of worldwide laboratory-confirmed influenza data from 1983 to 2008 showed that seasonal patterns in tropical countries vary widely: 56% of 32 countries had one annual influenza epidemic, 28% had biannual epidemics, 13% had triennial epidemics, and 3% had no seasonal pattern. In addition, only four (20%) of 20 tropical countries with multi-year data had peak influenza activity within the same 12 weeks each year.⁹ These data suggest that further information regarding seasonal influenza patterns in tropical countries is needed, and that public health efforts may need to be individualized for these countries.

1.2 Epidemiology of influenza in Sri Lanka

In Sri Lanka, acute lower respiratory infections are a leading cause of childhood morbidity and mortality, and are responsible for 9% of deaths in children under 5 years of age.¹⁰ In 2007, a total of 1,440 cases of influenza were reported in the country's Annual Health Bulletin, but the true impact of influenza in the country has been largely unknown due to limited surveillance.¹¹ A study by Perera *et al.* in 2003- 2004 showed

⁹ Azziz Baumgartner, E., Dao, C. N., Nasreen, S., Bhuiyan, M. U., Mah-E-Muneer, S., Al Mamun, A., ... Bresee, J. (2012). Seasonality, timing, and climate drivers of influenza activity worldwide. *The Journal of Infectious Diseases*, 206(6), 838–46.

¹⁰ World Health Organization. (2010). *Communicable Disease Epidemiological Profile- Sri Lanka*. Geneva.

¹¹ Sri Lanka Ministry of Health. (2007). *Annual Health Bulletin*. Colombo.

that influenza accounted for 11% of acute respiratory infections in patients presenting to Colombo North Teaching Hospital in Ragama, located in the Western Province.

Influenza A activity peaked in May- July 2003, with another minor peak in October-December 2003, and there was some correlation between influenza A activity and peak rainfall.¹²

In 2008, in response to the threat posed by H5N1 avian influenza, Sri Lanka's Ministry of Health initiated influenza surveillance in humans to complement animal surveillance by the Department of Animal Production and Health. This coordinated effort has grown in recent years and now includes surveillance for influenza-like illness (ILI) in the outpatient departments (OPDs) of 20 sentinel hospital sites, as well as surveillance for severe acute respiratory tract infection (SARI) in 3 sentinel hospital sites. In 2012, a total of 489 cases of influenza were confirmed by surveillance cultures in the country.¹³ However, little published data exist regarding seasonal patterns of influenza in Sri Lanka, or how these patterns vary in the diverse regions of the country. Influenza vaccination rates remain low, and availability of the vaccine is confined to the private sector.¹⁴

¹² Perera, K., Chan, K., Ma, E., & Peiris, J. (2010). Influenza virus infections among a sample of hospital attendees in Ragama, Sri Lanka. *Ceylon Med J*, 55(2), 40-4.

¹³ Epidemiology Unit, Ministry of Healthcare and Nutrition. (2013). *Influenza Surveillance* (pp. 1-2).

¹⁴ Attygalle, R. (2013, July 13). Getting vaccinated the proper way. *The Island*. Colombo.

1.3 Influenza, antibiotic use, and the impact of rapid diagnostic testing

The clinical diagnosis of influenza and other respiratory viral infections is difficult due to the nonspecific nature of symptoms, which include fever, cough, malaise, myalgias, and headache.¹⁵ In more developed settings such as the United States, acute respiratory tract infections (ARTIs) account for 75% of all antibiotics prescribed by office-based physicians, and over half of ambulatory care visits for ARTIs result in antibiotic prescriptions, many of which are unnecessary.^{16,17} In less developed settings, where laboratory confirmation of influenza is rare and outpatient antibiotic use is largely unregulated, inappropriate antibiotic prescriptions for ILI can be even more common. This is due to a multitude of factors including a lack of diagnostic testing, low level of awareness among clinicians, and potential patient expectations for antibiotics.¹⁸ The irrational use of antibiotics is linked to increased rates of antimicrobial resistance,

¹⁵ Woolpert, T., Brodine, S., Lemus, H., Waalen, J., Blair, P., & Faix, D. (2012). Determination of Clinical and Demographic Predictors of Laboratory-Confirmed Influenza with Subtype Analysis. *BMC infectious diseases*, 12(1), 129.

¹⁶ Gill, J. M., Fleischut, P., Haas, S., Pellini, B., Crawford, A., & Nash, D. B. (2006). Use of antibiotics for adult upper respiratory infections in outpatient settings: a national ambulatory network study. *Family medicine*, 38(5), 349–54.

¹⁷ Grijalva, C. G., Griffin, M. R., & Page, P. (2014). Antibiotic Prescription Rates for Acute Respiratory Tract Infections in US Ambulatory Settings. *JAMA*, 302(7), 758– 766.

¹⁸ Bhavnani, D., Phatinawin, L., Chantra, S., Olsen, S. J., & Simmerman, J. M. (2007). The Influence of Rapid Influenza Diagnostic Testing on Antibiotic Prescribing Patterns in Rural Thailand. *International Journal of Infectious Diseases*, 11(4), 355–9.

drug-related adverse effects, and healthcare-associated infections.¹⁹ Antimicrobial resistance in particular is a problem of global reach that is pressing in developing countries.²⁰

Commercially available rapid diagnostic kits, while potentially expensive, could provide valuable information regarding the etiology of infections such as acute febrile respiratory illnesses, and result in cost savings by reducing unnecessary antibiotic use and ancillary diagnostic testing. Retrospective, observational studies of adults and children in developed settings have revealed that rapid influenza testing can reduce antibiotic use, additional diagnostic testing, and length of hospitalization.^{21,22,23} In addition, two randomized, controlled trials of pediatric patients have shown that a positive rapid diagnosis of influenza A/B is associated with lower antibiotic use, fewer additional tests ordered, and decreased time in the emergency room.^{24,25} However, only

¹⁹ Holloway, K. A. (2011). Promoting the rational use of antibiotics. *Regional Health Forum*, 15(1), 122–130.

²⁰ Hawkey, P. M., & Jones, A. M. (2009). The changing epidemiology of resistance. *Journal of antimicrobial chemotherapy*, 64 Suppl 1, i3–10.

²¹ Falsey, A. R., Murata, Y., & Walsh, E. E. (2007). Impact of Rapid Diagnosis on Management of Adults Hospitalized With Influenza. *Archives of Internal Medicine*, 167, 354–360.

²² Noyola, D. E., & Demmler, G. J. (2000). Effect of Rapid Diagnosis on Management of Influenza A infections, 19(4), 303–307.

²³ Donnelly, J. P., Baddley, J. W., & Wang, H. E. (2014). Antibiotic utilization for acute respiratory tract infections in U.S. emergency departments. *Antimicrobial Agents and Chemotherapy*, 58(3), 1451–7.

²⁴ Bonner, A. B., Monroe, K. W., Talley, L. I., Klasner, A. E., & Kimberlin, D. W. (2003). Impact of the Rapid Diagnosis of Influenza on Physician Decision-Making and Patient Management in the Pediatric

one study to date has explored the use of rapid tests in less developed settings, where antibiotic use is generally more prevalent and less regulated. In a retrospective observational study, Bhavnani *et al.* showed that the use of rapid influenza tests in rural Thailand was associated with fewer antibiotic prescriptions for adults and children with ILI presenting to outpatient settings.²⁶ Studies in Sri Lanka, where outpatient antibiotic use is widespread and antimicrobial resistance appears to be rising, are lacking.

Emergency Department: Results of a Randomized, Prospective, Controlled Trial. *Pediatrics*, 112, 363–367.

²⁵ Esposito, S., Marchisio, P., Morelli, P., Crovari, P., & Principi, N. (2003). Effect of a Rapid Influenza Diagnosis. *Archives of Disease in Childhood*, 88(6), 525–6.

²⁶ Bhavnani, D., Phatinawin, L., Chantra, S., Olsen, S. J., & Simmerman, J. M. (2007). The Influence of Rapid Influenza Diagnostic Testing on Antibiotic Prescribing Patterns in Rural Thailand. *International Journal of Infectious Diseases*, 11(4), 355–9.

2. Objectives

- Primary:
 - to determine if access to rapid influenza test results was associated with fewer antibiotic prescriptions for outpatients with ILI in southern Sri Lanka
- Secondary:
 - to determine the seasonality and proportionality of ILI due to influenza in outpatients seeking care in southern Sri Lanka
 - to compare sociodemographic characteristics, environmental exposures, and clinical characteristics of outpatients with influenza versus ILI due to other etiologies
 - to describe the impact of illness on finances and productivity among outpatients with influenza versus ILI due to other etiologies
 - to describe the clinical diagnoses and treatment received by outpatients with ILI who were rapid-influenza positive versus rapid-influenza negative

3. Setting

3.1 Background on Sri Lanka and its healthcare infrastructure

Sri Lanka is a lower middle-income country (LMIC) with a population of 20,328,000 and a gross national income of \$2920 per capita.¹ Health metrics in the country parallel those of more developed nations, with average life expectancy of 75 years, under-five mortality of 10 per 1000 live births, and maternal mortality of 35 per 100,000. The total expenditure on health as percentage of GDP was 3.2% in 2012. From a public health standpoint, the country has made progress in reducing many childhood vaccine-preventable diseases, with estimates of 99% coverage for vaccines such as DTP, measles, and Hib.² Great progress has been made in eradicating infections such as leprosy, malaria, and lymphatic filariasis, but dengue, leptospirosis, and leishmaniasis continue to be prevalent, and both noncommunicable diseases and traumatic injuries are on the rise.

The health sector in Sri Lanka is composed of both public and private services. The public health sector provides preventative and curative services free of charge to the entire population, while the private sector provides mainly curative services and is

¹ The World Bank. (2014). Sri Lanka. Retrieved June 28, 2014, from <http://data.worldbank.org/country/sri-lanka>

² World Health Organization. (2013). *Sri Lanka- Country cooperation strategy at a glance*.

concentrated in urban and suburban areas.³ In 2009, there were approximately 1638 health facilities in the public sector and 186 health facilities in the private sector.

Hospitals in the public sector are organized according to a tiered structure based on services available, with primary care provided by central dispensaries, rural hospitals, and district hospitals, secondary care provide by base and general hospitals, and tertiary care provided by teaching hospitals and special hospitals. In 2009, it was estimated that there were 5,473,884 admissions to public facilities in the country. Of these, the highest number (6.4%) were due to unspecified viral illnesses.⁴

3.2 Duke-Ruhuna Collaboration

The research and educational collaboration between Duke University School of Medicine and Ruhuna University Faculty of Medicine was forged in early 2006, in the aftermath of the tsunami disaster.⁵ Investigators from Johns Hopkins University School of Medicine joined this collaboration in 2007. The Faculty of Medicine and its associated hospital, Teaching Hospital Karapitiya (THK), are located in Galle, a coastal city in the Southern Province of Sri Lanka. The Galle municipality area has a population of 112,252

³ Epidemiology Unit, Ministry of Health. (2005). *Influenza pandemic preparedness and response*. *AJN, American Journal of Nursing* (Vol. 105, pp. 73–74). Colombo.

⁴ Department of Census & Statistics. (2012). *Sri Lanka Census of Population and Housing, 2011*. Retrieved May 09, 2014, from <http://www.statistics.gov.lk/PopHouSat/CPH2011/index.php?fileName=pop32&gp=Activities&tpl=3>

⁵ Duke University School of Medicine. (2011). *Teaching Hospital at Karapitiya*. Retrieved May 31, 2014, from <http://dukeglobalhealth.org/global-partners/sri-lanka>

and a land area of 16.5km², and is bordered by the Indian Ocean along its south and southwest edges.⁶ THK is the largest tertiary care center in the Southern Province, consisting of 1560 beds and 54 wards, and receives referrals from throughout the province. The hospital provides basic medical, surgical, and psychiatric care, and also has specialty services such as cardiothoracic surgery, neurosurgery, dermatology, oncology, and radiology capacity including CT and MRI.⁷

⁶ Galle Municipal Council. (2010). Galle Municipal Council. Retrieved May 31, 2014, from <http://www.galle.mc.gov.lk/>

⁷ University of Ruhuna, F. of M. (n.d.). Karapitiya Teaching Hospital. Retrieved April 28, 2014, from <http://www.medi.ruh.ac.lk/THK/index.php>

4. Methods

4.1 Study setting

This pretest- posttest study was conducted in the Outpatient Department (OPD) of Teaching Hospital Karapitiya, the largest tertiary care hospital in the Southern Province of Sri Lanka. The OPD of this hospital serves over 1000 patients daily, and provides care between the hours of 8a and 7p.

4.2 Study procedures

All adults and children presenting to the OPD at THK were surveyed for the presence of ILI by an MBBS-qualified physician (pre-intern). Surveillance began in March 2013 and is ongoing to date; surveillance was paused between December 2013 and mid-January 2014 due to lack of staffing. Approximate times of surveillance included 8a- 12p and 1p-3p on Monday to Friday, and 8a to 12p on Saturday. The following criteria were used for enrollment:

Inclusion criteria:

- Age \geq 1 year
- Presence of ILI as defined by the World Health Organization: fever (tympanic temperature \geq 38°C/ 100.4°F) and acute onset of cough in the past seven days without alternative diagnosis¹

¹ World Health Organization. (2012). *WHO Interim Global Epidemiological Surveillance Standards for Influenza*.

Exclusion criteria:

- Patients unable or unwilling to give consent

The physician research assistant screened all patients with acute onset of cough for the presence of fever. Patients meeting the definition of ILI were offered participation in the study, with consent being obtained from patients ≥ 18 years of age and the guardians of patients < 18 years, and assent being obtained from patients 12- 17 years. Enrolled patients were administered a standardized questionnaire (Appendix A) in the local language of Sinhala, and a physical examination was conducted. Two nasopharyngeal samples were collected from all patients, with patients unable to tolerate nasopharyngeal swab collection having two nasal samples collected instead. Patients received standard clinical evaluation including physical exam, prescriptions, and additional diagnostic testing from their routine care providers in the OPD. Details regarding patients' clinical diagnoses and management were recorded. Study personnel were not involved in clinical decision-making or treatment at any point.

4.3 Sample processing

One nasal/ nasopharyngeal sample was used immediately for rapid influenza testing using the Becton Dickinson Veritor Flu A+B system. This rapid chromatographic

immunoassay detects influenza A and B viral nucleoprotein antigens from nasal and nasopharyngeal swabs using a single processed sample, with all necessary reagents and supplies provided in the kit. Once a nasal/ nasopharyngeal sample was obtained from the patient, the swab was placed into a reagent tube containing 400 μ L of detergent with <0.1% sodium azide. This reagent was then placed into the sample well of a test strip containing influenza antibodies conjugated to detector particles. If positive for influenza, the influenza antigen-antibody complex would migrate across the test strip to the appropriate reaction area ("A" position for influenza A, "B" position for influenza B) and a negative control within the device would migrate to the "C" (control) position. Following 10 minutes for reaction time, the test device was inserted into a 8 x 6 x 12cm battery-powered reader which weighed 0.5kg, with the result being available immediately.

The performance characteristics of the Veritor System were established during the 2010- 2011 influenza season at 5 sites in the US and 8 sites in Japan. When compared to polymerase chain reaction (PCR) results from the same patients, the sensitivity and specificity of the test was 78.7% and 97.8%, respectively, for influenza A, and 74.3% and 99.5%, respectively, for influenza B in the US. At the Japanese sites, the sensitivity and

specificity of the test was 94.4% and 96.7%, respectively, for influenza A, and 91.4% and 94.7%, respectively, for influenza B.²

The second nasal/ nasopharyngeal sample obtained from the patient was immediately placed into a pre-labeled vial containing approximately 3mL of viral transport media and transferred to the Microbiology Laboratory at the Department of Microbiology, Faculty of Medicine, University of Ruhuna for processing. Samples were separated into 1ml aliquots in the laboratory and frozen at -70⁰ C. PCR testing will be carried out on these specimens at a future date to assess for the presence of influenza A, B, and C, as well as other respiratory viruses such as parainfluenza virus, adenovirus, and respiratory syncytial virus.

4.4 Study design

This study was conducted using a pretest-posttest design, in order to determine the impact of releasing influenza results on clinicians' prescription of antibiotics. During the initial phase of the study (March 2013- November 2013), rapid influenza testing was performed on all patients after they had seen their routine care providers in the OPD. Neither patients nor their clinicians were provided with a result from the rapid influenza testing. During the second phase of the study (December 2013- ongoing),

² Becton Dickinson. (2014). BD Veritor System - CLIA-waived for rapid detection of Flu A+B. Retrieved May 31, 2014, from <http://www.bd.com/ds/productCenter/256045.asp>

enrollment and rapid influenza testing were performed prior to the patient seeing the OPD physician, and both the patient and the physician were provided with the rapid influenza test result. In both phases of the study, the prescription of antibiotics and the ordering of ancillary diagnostic tests by clinicians were recorded. Prior to the second phase of the study, an informational session was conducted with physicians in the OPD regarding the provision of rapid influenza test results and the performance characteristics of the test.

4.5 Analysis plan

The study was designed to test the hypothesis that rapid influenza testing would be associated with a decrease in antibiotic prescriptions among outpatients presenting with ILI. In order to detect a 15% decrease in antibiotic use, assuming a baseline rate of 80% antibiotic use in the influenza group and overall influenza positivity of 50%, with 80% power at 95% significance, a sample of 302 patients was required in each of the pre and post arms.

The proportion of patients positive for influenza using the rapid test was calculated. Patient characteristics between the two phases were compared using the Fisher's exact test for categorical variables and the Kruskal-Wallis test for continuous variables. Odds ratios and 95% confidence intervals were calculated by bivariable and multivariable logistic regression for the association between rapid influenza test positivity and patients' sociodemographic characteristics, animal/ vector and sick

contact exposures, clinical signs and symptoms, clinical diagnoses and treatment received, and impact on finances and productivity. In addition, odds ratios and 95% confidence intervals were calculated by bivariable and multivariable methods for the association between antibiotic prescriptions and patients' sociodemographic characteristics, clinical signs and symptoms, clinical diagnoses and treatment received, clinicians' knowledge of rapid influenza test positivity, and impact on finances and productivity. Two-sided p-values were calculated for all results.

4.6 Ethical considerations

Ethical approval for this study was obtained from the Duke University Institutional Review Board, Johns Hopkins Medicine Institutional Review Board, and Ruhuna University Ethical Review Committee. In addition, the Sri Lanka Ministry of Health and the Director of Teaching Hospital Karapitiya both approved the release of rapid influenza test results for clinical purposes during the second phase of this study.

5. Results

During the period from March 2013 to April 2014, a total of 45,984 consecutive patients ≥ 1 year old were screened in the Outpatient Department: 38,555 (83.8%) were adults ≥ 12 years, with 37.8% of adults and 54.4% of children being male (patients 12 years of age and greater are admitted to adult wards in this hospital). Of all screened patients, a total of 4143 (9.0%) had a history of acute cough in the previous seven days and 408 (0.9%) were eligible by recorded temperature criteria (tympanic temperature $\geq 100.4^{\circ}\text{F}$) and history of acute cough with no alternate cause. Of those who were eligible, 397 (97.3%) patients consented and were enrolled in the study. Figure 1 shows a flow diagram of patients who were screened, eligible, and enrolled, listed by age and sex. There was no statistically significant difference between proportions of patients eligible and enrolled by age and sex ($p = .91$). Figure 2 shows a graphical representation of the number of patients screened and enrolled each month.

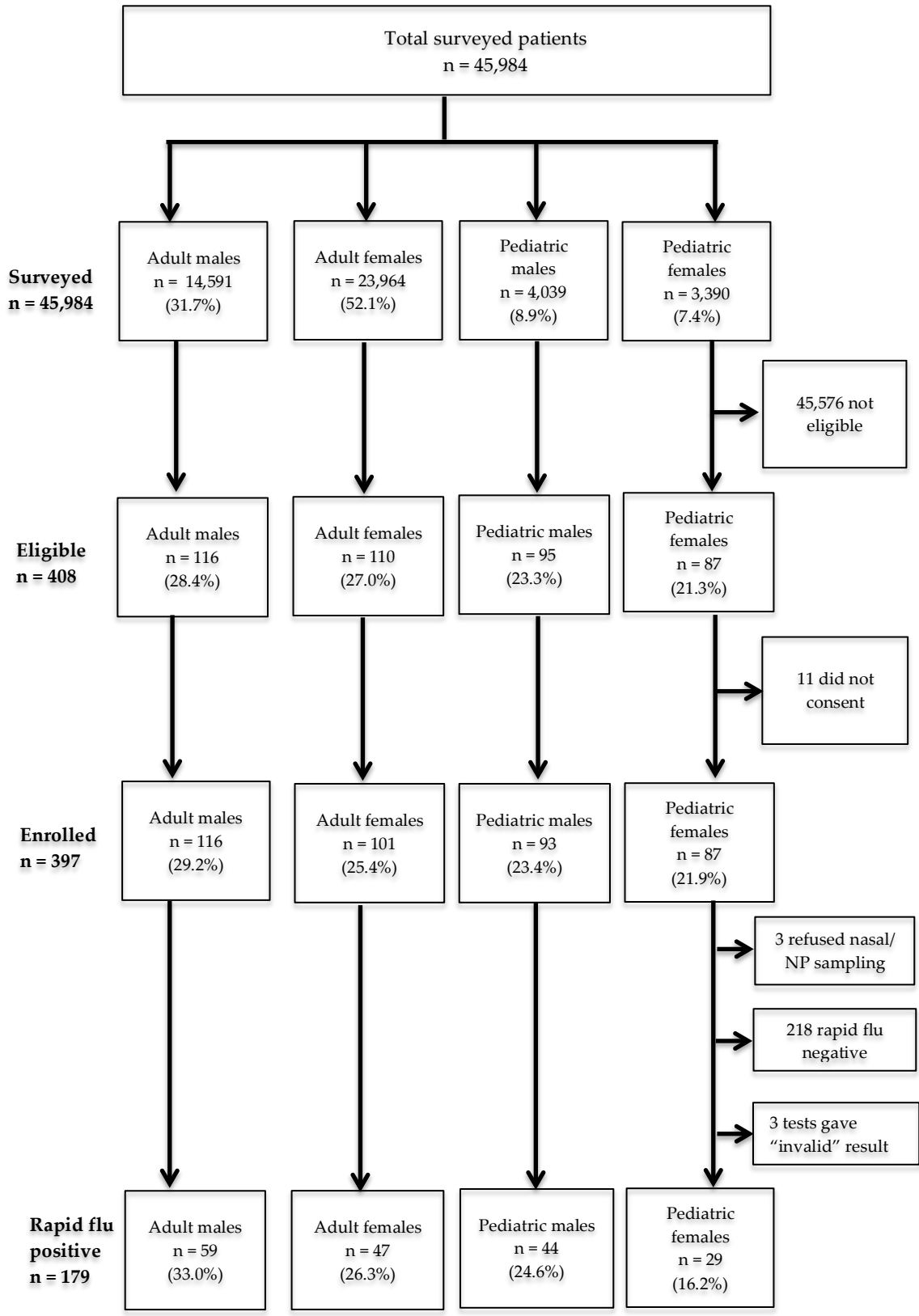


Figure 1: Flow chart depicting patients who were screened, eligible, enrolled, and positive for influenza among patients presenting to an Outpatient Department in southern Sri Lanka from March 2013- April 2014. Adult is ≥ 12 years of age, which is the age criterion used for admission to the adult wards at this hospital.

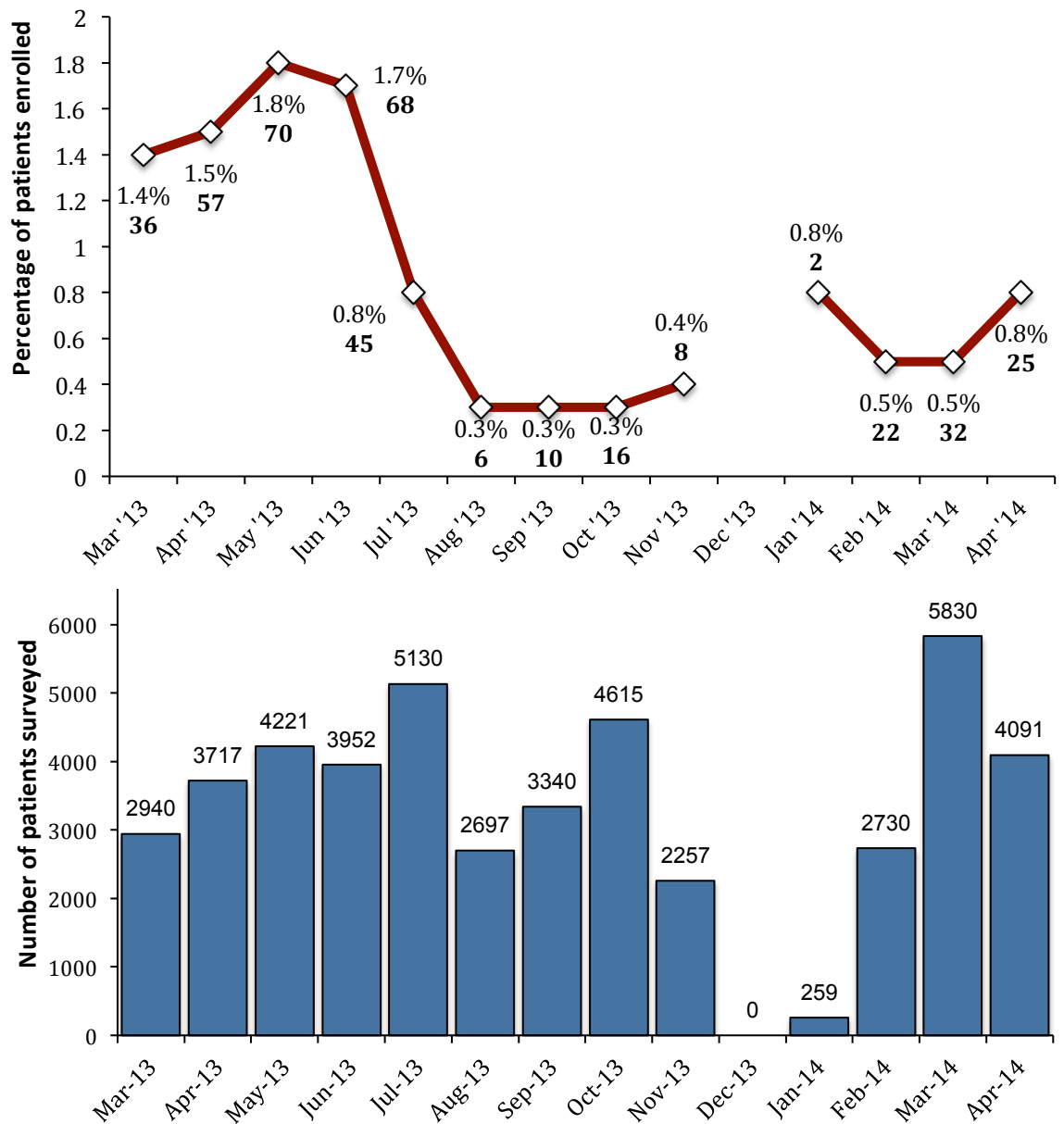


Figure 2: Lower graph: number of patients screened for ILI in the OPD at Teaching Hospital Karapitiya from March 2013- April 2014, listed by month. Upper graph: percentage of screened patients with ILI who were enrolled, listed by month. The absolute number of patients enrolled each month is listed under the percentage.

5.1. Description of study population

5.1.1 Sociodemographic characteristics

Table 1 lists the sociodemographic characteristics of enrolled patients. Of 397 total patients, the proportion of adults was slightly higher, with 217 (54.7%) patients being adults ≥ 12 years. Figure 3 depicts the distribution of ages for all enrolled patients. Median (IQR) age was 13.7 (6.1- 38.0) years, and approximately half of patients (209, 52.6%) were male.

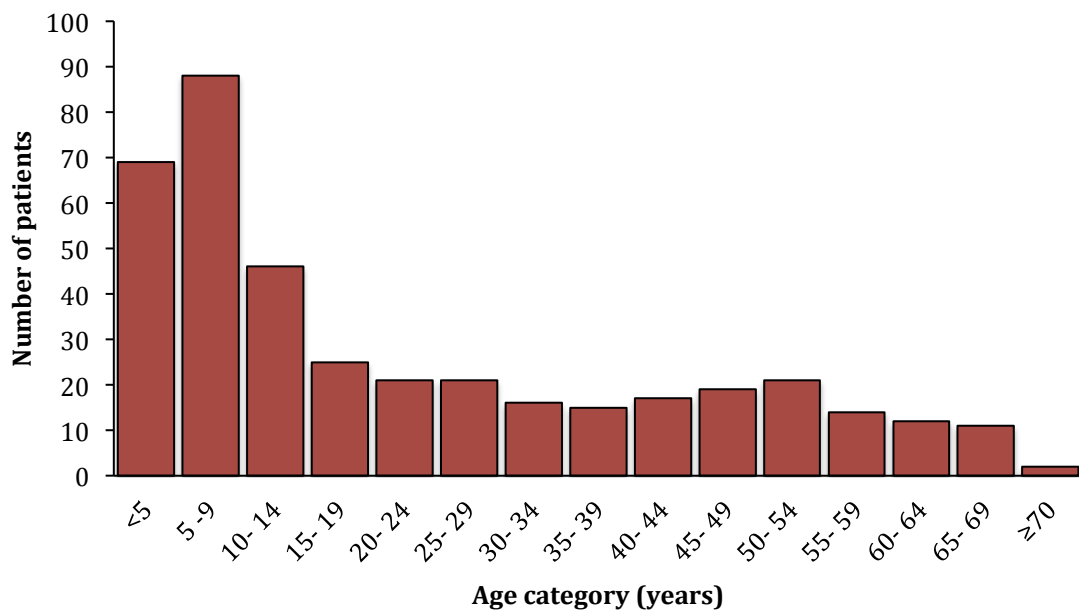


Figure 3: Age distribution of patients enrolled with ILI in southern Sri Lanka from March 2013- April 2014.

The most common hometown of residence was Galle, with 91 (22.9%) of patients; other common hometowns included Poddala with 42 (10.6%) patients, Akmeemana with 31 (7.8%) of patients, and Wanduramba with 15 (3.8%) of patients. Figure 4 shows a map

of southern Sri Lanka and the common hometowns of patients. The median (IQR) distance traveled to THK was 5.8 (3.0- 15.0) km, and the median (IQR) time traveled to THK was 30.0 (15.0- 45.0) minutes.

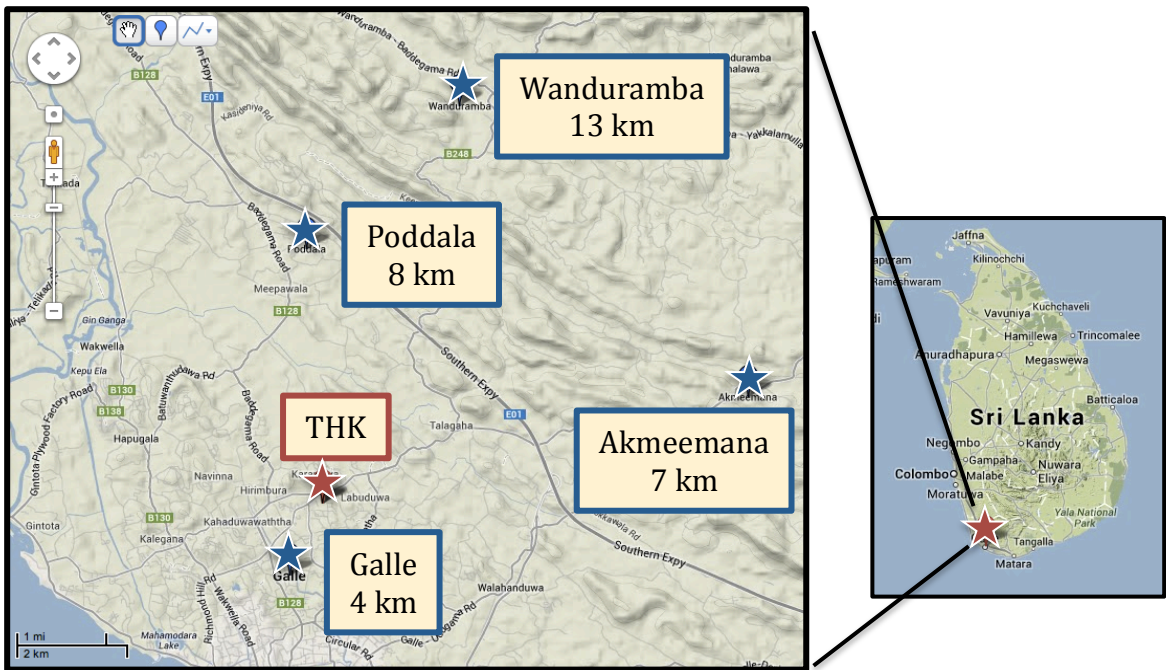


Figure 4: Map of southern Sri Lanka with the most common hometowns of patients, among outpatients with ILI enrolled from March 2013- April 2014.

Source: <https://maps.google.com>.

Most patients did not have higher-level education. Among patients ≥ 18 years, 32.8% (59) reported less than an O/L (10th grade) education, 66 (36.7%) reported only an O/L education, and 54 (30.0%) reported an A/L (12th grade) education or higher. Of

adults, most (45, 25.0%) were housewives, followed by merchant/ shop/ office worker (34, 18.9%), laborer/ factory worker (25, 13.9%), and farmer/ agricultural laborer (18, 10.0%). A total of 16 (8.9%) were unemployed.

Table 1: Sociodemographic characteristics of outpatients enrolled with ILI in southern Sri Lanka from March 2013- April 2014, listed for the entire study population as well as for each phase of the study.

	All patients n=397	First phase n=311	Second phase n=86	p- value*
	Frequency (percent) or median (IQR)			
Age (years)	13.7 (6.1- 38.0)	13.9 (6.5- 38.3)	13.7 (5.3- 37.5)	.42
Adults ≥12 years	217 (54.7%)	172 (55.3%)	54 (52.3%)	1.00
Male	209 (52.6%)	172 (55.3%)	37 (43.0%)	.05
Hometown				
Galle	91 (22.9%)	71 (22.8%)	20 (23.4%)	.04
Poddala	42 (10.6%)	39 (12.5%)	3 (3.5%)	
Akmeemana	31 (7.8%)	22 (7.1%)	9 (10.5%)	
Wanduramba	15 (3.8%)	14 (4.5%)	1 (1.2%)	
Distance to THK (km)	5.8 (3.0- 15.0)	5.0 (3.0- 15.0)	8.0 (3.0- 20.0)	.59
Time to THK (mins)	30.0 (15.0- 45.0)	30.0 (15.0- 60.0)	20.0 (15.0- 30.0)	.06
Occupation (adults ≥18 years)				
Housewife	45 (25.0%)	29 (20.6%)	16 (41.0%)	.001
Merchant/ shop/ office worker	34 (18.9%)	31 (22.0%)	3 (7.7%)	
Laborer/ factory worker	25 (13.9%)	22 (15.6%)	3 (7.7%)	
Farmer/ agricultural	18 (10.0%)	10 (7.1%)	8 (20.5%)	
Unemployed	16 (8.9%)	16 (11.4%)	0 (0.0%)	
Education (adults)				
<O/L	59 (32.8%)	48 (34.0%)	11 (28.2%)	.56
O/L	66 (36.7%)	52 (36.9%)	14 (35.9%)	
A/L	38 (21.1%)	27 (19.2%)	11 (28.2%)	
>A/L	16 (8.9%)	14 (9.9%)	2 (5.1%)	

* Characteristics between the two phases are compared, using Fisher's exact test for categorical variables and the Kruskal-Wallis test for continuous variables.

5.1.2 Exposures and risk factors

The most common animal/ vector exposure reported was mosquitoes (382, 96.2%), followed by dogs (221, 55.7%) and cats (208, 52.4%). A total of 74 (18.7%) patients reported exposure to passive smoke, while another 29 (7.3%) were active smokers. The most common comorbid condition was asthma, present in 33 (8.3%) of patients.

Almost half of patients (172, 43.3%) reported a recent sick contact with similar illness. For these patients, within the past one week was the most common time of exposure (144, 83.7%) and the most common location of sick exposure was at home (160 (93.0%). Only 57 (14.4%) of patients reported travel within the past 30 days, with the majority of these (37, 64.9%) reporting travel that was within the Southern Province. See Table 2 for exposures listed for the whole study population, as well as by phase of study.

Table 2: Exposures and risk factors for outpatients with ILI in southern Sri Lanka, March 2013- April 2014, listed for the entire study population as well as for each phase of the study.

	All patients n=397	First phase n=311	Second phase n=86	p-value*
	Frequency (percent) or mean (range)			
Animal exposures				
Dogs	221 (55.7%)	201 (64.6%)	20 (23.3%)	<.001
Cats	208 (52.4%)	186 (59.8%)	22 (25.6%)	<.001
Mosquitoes	382 (96.2%)	298 (95.8%)	84 (97.7%)	.54
Birds	20 (5.0%)	19 (6.1%)	1 (1.2%)	.09
Smoking exposure				
Active	29 (7.3%)	25 (8.0%)	4 (4.7%)	.03
Passive	74 (18.6%)	64 (20.6%)	10 (11.6%)	
Sick contact				
Home	160 (40.3%)	130 (41.8%)	30 (34.9%)	.27
Work/ school	17 (4.3%)	7 (2.3%)	10 (11.6%)	.001
Weeks prior	1.3 (1.0- 4.0)	1.1 (1.0- 4.0)	1.8 (1.0- 2.0)	<.001
Travel				
Provincial	37 (9.3%)	34 (10.9%)	3 (3.5%)	.002
Outside Province	20 (5.0%)	20 (6.4%)	0 (0.0%)	

* Characteristics between the two phases are compared, using Fisher's exact test for categorical variables and the Kruskal-Wallis test for continuous variables.

5.1.3 Prior care

Only a quarter (104, 26.2%) of patients reported a prior visit for the same illness, with the most common prior visit type being to a general practitioner (55, 52.9% of visits) or to an Outpatient Department (49, 47.1%). Only 18 (4.5%) reported receiving an antimicrobial for the same illness prior to presentation. However, another 68 (17.2%) reported being unsure about the receipt of an antibiotic. No patients reported receiving an influenza vaccine previously.

5.1.4 Clinical presentation

A total of 337 (84.9%) patients reported fever as being the primary symptom that brought them to the hospital. Eighty-eight (22.2%) of patients reported cough as being the primary symptom that brought them to the hospital (44 patients listed both fever and cough as the primary symptoms). The median (IQR) time of onset for the primary symptom was 2.0 (2.0- 4.0) days. The median duration of fever was 2.0 (1.0- 3.0) days, and the median duration of cough was 2.0 (2.0- 3.0) days. Common symptoms besides cough and fever included fatigue/ lethargy in 298 (75.1%) patients, headache in 298 (75.1%) patients, decreased appetite in 285 (71.8%) patients, myalgia in 277 (69.8%) patients, arthralgia in 272 (68.5%) patients, rhinitis/ congestion in 265 (66.8%) patients, sore throat in 187 (47.1%) patients, and shortness of breath in 85 (21.4%) patients. On exam, the mean temperature was 101.3F. Among adults ≥ 12 , the median respiratory rate was 18 (14- 20) and the median heart rate was 100 (88- 112). The median O_2 saturation among all patients was 100% (99%-100%). Normal breath sounds on examination were present in 392 (98.7%) of patients (see Table 3).

Table 3: Clinical symptoms, exam findings, and clinical diagnoses and treatment received among outpatients with ILI in southern Sri Lanka, March 2013 to April 2014. Fever and cough were experienced by all patients.

	All patients n=397	First phase n=311	Second phase n=86	p- value*
	Frequency (percent) or median (IQR)			
Clinical symptoms				
1° symptom days	2 (2- 4)	2 (2- 3)	3 (2- 5)	<.001
Fever days	2 (1- 3)	2 (1- 3)	2 (2- 3)	<.001
Cough days	2 (2- 3)	2 (1- 3)	3 (2- 4)	.001
Fatigue/ lethargy	298 (75.1%)	256 (82.3%)	42 (48.8%)	<.001
Headache	298 (75.1%)	246 (79.1%)	52 (60.5%)	.001
Decreased appetite	285 (71.8%)	240 (77.2%)	45 (52.3%)	<.001
Myalgias	277 (69.8%)	228 (73.3%)	49 (57.0%)	.01
Arthralgias	272 (68.5%)	222 (71.4%)	50 (58.1%)	.03
Rhinitis/ congestion	265 (66.8%)	186 (59.8%)	79 (91.9%)	<.001
Sore throat	187 (47.1%)	155 (49.8%)	32 (37.2%)	.04
Shortness of breath	85 (21.4%)	84 (27.0%)	1 (1.2%)	<.001
Vomiting	79 (19.9%)	64 (20.6%)	15 (17.4%)	.65
Pleuritic chest pain	55 (13.9%)	53 (17.0%)	2 (2.3%)	<.001
Abdominal pain	27 (6.8%)	22 (7.1%)	5 (5.8%)	.81
Exam findings				
Temperature (°F)	101.1 (100.6- 101.9)	101.1 (100.7- 101.9)	100.8 (100.4- 101.9)	.04
Respiratory rate (adults ≥12 yrs)	18 (14- 20)	18 (14- 20)	17 (16- 20)	.20
Heart rate (adults ≥12 yrs)	100 (88- 112)	100 (88- 120)	78 (73- 88)	<.001
O ₂ saturation (%)	100 (99- 100)	100 (99- 100)	100 (100-100)	<.001
Normal breath sounds	392 (98.7%)	308 (99.0%)	84 (97.7%)	.30
Care received				
Clinical diagnoses				
Unspecified viral fever	155 (39.0%)	142 (45.7%)	13 (15.1%)	<.001
Upper respiratory Infection	100 (25.2%)	66 (21.2%)	34 (39.5%)	.001

Lower respiratory infection	58 (14.6%)	45 (14.5%)	13 (15.1%)	.86
Influenza	26 (0.0%)	0 (0.0%)	26 (30.2%)	<.001
Antibiotic prescribed	310 (78.1%)	253 (81.4%)	57 (66.3%)	.01
Additional diagnostic test ordered	72 (18.1%)	64 (20.6%)	8 (9.3%)	.02

* Characteristics between the two phases are compared, using Fisher's exact test for categorical variables and the Kruskal-Wallis test for continuous variables.

5.1.5 Rapid influenza test results

Of 397 patients who were enrolled, a total of 179 (45.8%) of patients tested positive for influenza by rapid lateral flow testing: 124 (69.3% of positives) for influenza A and 55 (30.7%) for influenza B. Figure 5 shows the distribution of patients with ILI and influenza enrolled per month, and Figure 6 shows the number of cases per month by influenza type. Influenza cases peaked from April to July 2013, with low levels of activity from September to November 2013. Approximately one-third of influenza cases during the larger peak from April to July 2013 were due to influenza B. Figure 7 shows the monthly variation in rapid influenza-positive cases, plotted against average monthly high temperature, low temperature, and rainfall in Galle. Although no correlation is seen with temperature, influenza cases appear to be highest during the two rainy seasons in this region.

Three patients (0.8% of total) had tests that returned as 'invalid,' and 3 patients (0.8%) patients refused rapid testing following consent. Of the 391 patients who received valid rapid influenza test results, 344 (86.6%) were tested using nasopharyngeal samples, whereas 50 (12.6%) were tested using nasal samples.

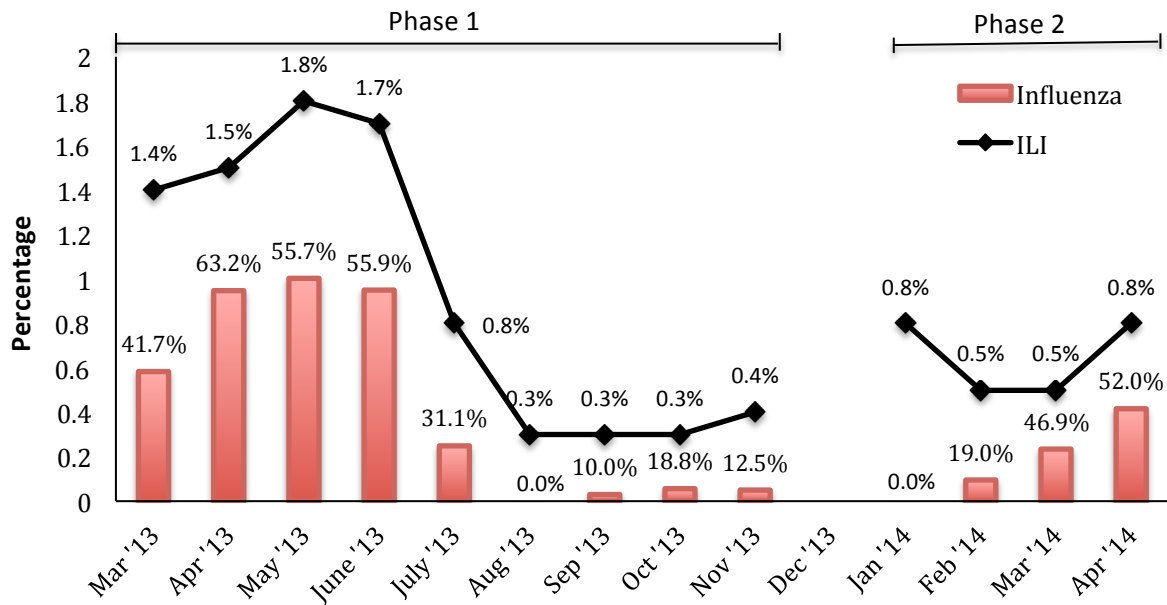


Figure 5: Enrolled ILI cases and rapid influenza-positive cases in southern Sri Lanka, March 2013 to April 2014. The percentage of ILI cases out of total screened patients is depicted by the line graph. The bars indicate the percentage of ILI cases that were positive for influenza by rapid influenza testing.

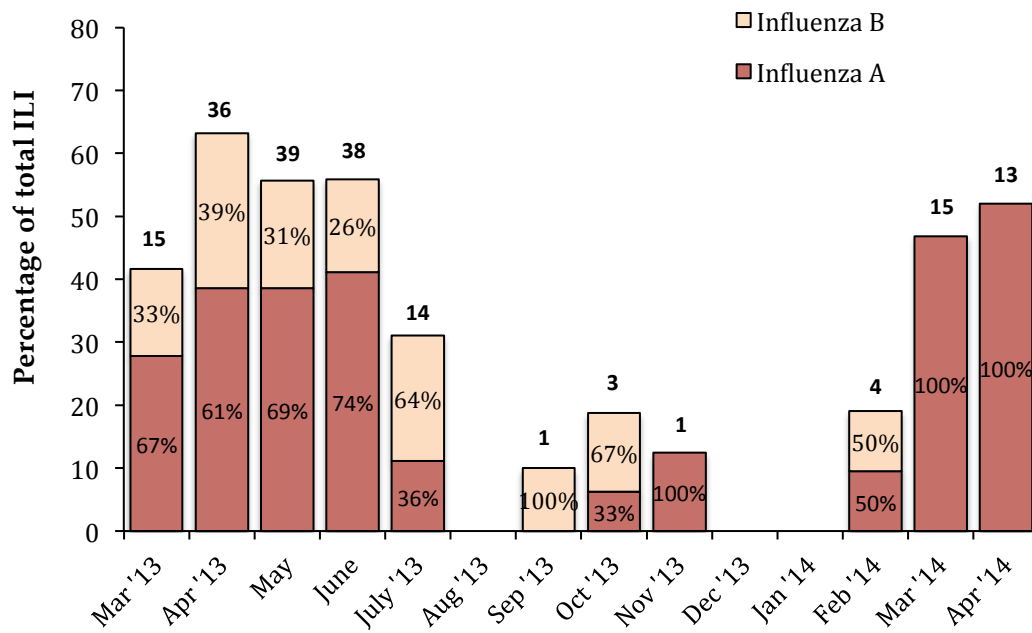


Figure 6: ILI and influenza cases in southern Sri Lanka, depicted over time from March 2013- April 2014. The percentage of total ILI cases due to influenza are shown by the bars, with the proportion of influenza due to influenza A depicted in red and the proportion of influenza due to influenza B depicted in yellow. The total numbers of patients who tested positive for influenza by rapid testing are listed above the bars.

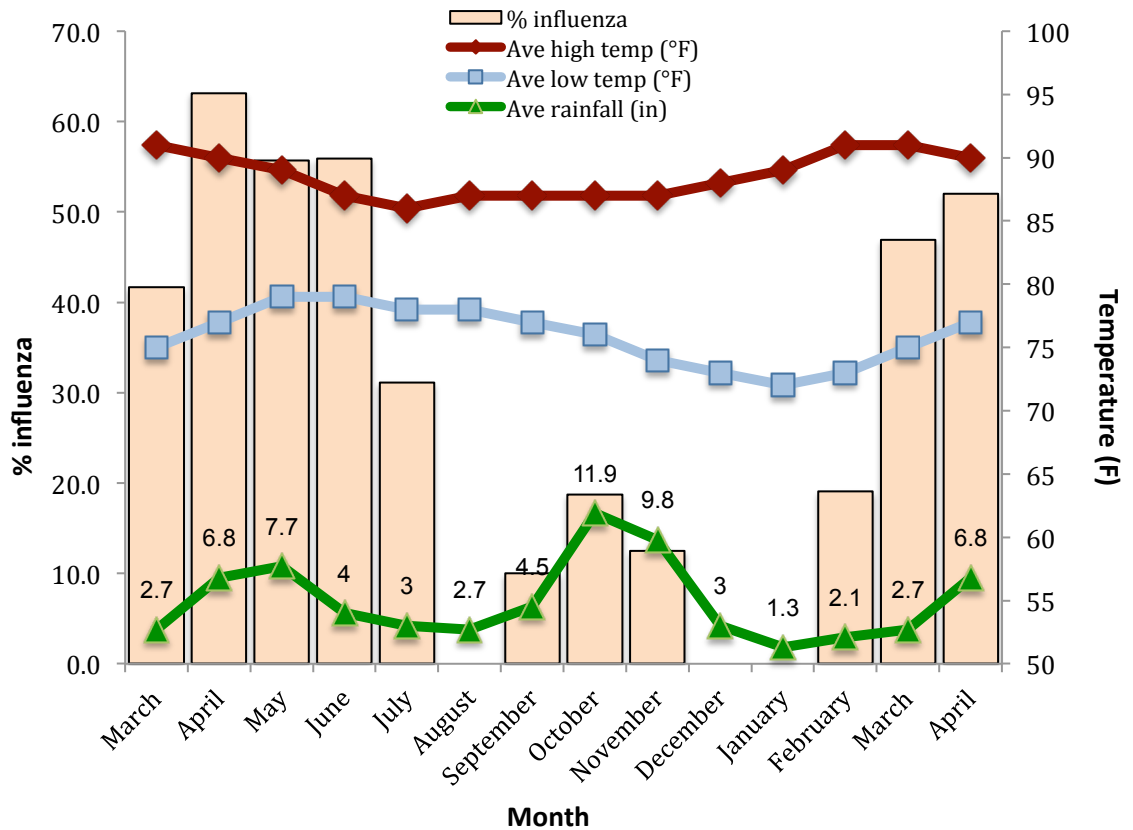


Figure 7: Monthly fluctuations in proportion of rapid influenza positive cases and weather indicators for Galle, Sri Lanka. Average monthly high and low temperatures (°F) and average rainfall (inches) in Galle are depicted by the line graphs. The monthly percentage of ILI cases that were positive for influenza are depicted by the bars. Climate data obtained from <http://www.worldweatheronline.com/Galle-weather-averages/Southern/LK.aspx>.

5.1.6 Clinical management

The most common clinical diagnoses by clinicians included unspecified viral fever in 155 (39.0%) patients, followed by upper respiratory infection in 100 (25.2%) and lower respiratory infection in 58 (14.6%) patients. A total of 310 (78.1%) received a prescription for an antibiotic from the outpatient physician. The most common types of antibiotics prescribed were penicillin/ amoxicillin in 200 (50.4%) of patients, a first-generation cephalosporin in 77 (19.4%), erythromycin in 16 (4.0%), and a fluoroquinolone in 9 (2.3%). No patients were admitted for treatment with antiviral therapy (antivirals are not available through the outpatient pharmacy, but are available to inpatients). Additional diagnostic tests were ordered in 72 (18.1%) of patients. The most common diagnostic test ordered was a full blood count in 66 patients (91.7% of tests).

5.1.7 Impact on finances and productivity

The main financial burden associated with patients' illness was due to travel, since most patients had not sought prior care for their illness. The mean amount spent on prior medication for the same illness was 40 Rs (0.30 USD), while the mean amount spent on a prior medical visit for the same illness was 17 Rs (0.13 USD).¹ The mean cost

¹ Central Bank of Sri Lanka. (2014). Current Economic Indicators. Retrieved June 29, 2014, from http://www.cbsl.gov.lk/htm/english/_cei/er/e_1.asp

of travel for the illness (including for the current visit) was 105 Rs (0.81 USD). Loss of productivity due to illness was low, with the mean (median) days of work or school missed by adults ≥ 18 years being 1.2 (1.0) days and the mean days of school missed by children < 18 years being 1.2 (1.0) days (Table 4).

Table 4: Impact of illness on finances and productivity among outpatients with ILI in southern Sri Lanka from March 2013- April 2014, listed for the total study population as well as for each phase of the study.

	All patients n=397	First phase n=311	Second phase n=86	p- value*
	Frequency (percent) or mean (range)			
Rupees spent on medications	39.6 (0.0- 1200.0)	37.1 (0.0- 1200.0)	48.3 (0.0- 700.0)	.54
Rupees spent on prior visits	16.9 (0.0- 700.0)	11.6 (0.0- 400.0)	36.0 (0.0- 700.0)	.02
Rupees spent on travel for care	105.1 (0.0- 1000.0)	102.8 (0.0-1000.0)	113.0 (0.0- 300.0)	.002
Work days missed (patients ≥ 18 yrs)	1.2 (0.0- 14.0)	1.3 (0.0- 14.0)	0.9 (0.0- 5.0)	.43
School days missed (< 18 yrs)	1.2 (0.0- 11.0)	1.2 (0.0- 11.0)	1.1 (0.0- 4.0)	.71

* Characteristics between the two phases are compared, using Fisher's exact test for categorical variables and the Kruskal-Wallis test for continuous variables.

5.2 Comparison of first and second phases

5.2.1 Sociodemographic characteristics, exposures, and impact on finances and productivity

There were several significant differences in baseline sociodemographic characteristics, exposures, and cost/ productivity impact between the first and second phases. As shown in Table 1, patients in the first phase were more likely to be from

Poddala or Wanduramba ($p=.04$) and to be merchant/shop/office workers, laborers/factory workers, or unemployed ($p=.001$). Patients in the first phase were also more likely to report dog and cat exposures ($p<.001$), to have a history of active or passive smoking ($p=.03$), and to report a history of travel in the previous 30 days ($p=.002$). In addition, they were less likely to report a sick contact at work or school ($p=.001$), although their reported sick contacts were more recent ($p<.001$). Finally, patients in the first phase of the study spent less on prior medical visits and travel ($p=.02$ and $.002$, respectively).

5.2.2 Clinical characteristics and physical exam findings

There were significant differences in the clinical characteristics of patients between the first and second phases. Patients in the first phase had a shorter duration of primary symptom and fever prior to presentation ($p<.001$), as well as a shorter duration of cough ($p=.001$). In addition, patients in the first phase were more likely to experience fatigue/ lethargy, decreased appetite, shortness of breath, and pain with breathing ($p<.001$). They also reported a higher incidence of headache ($p=.001$), myalgias ($p=.01$), arthralgias ($p=.03$), and sore throat ($p=.04$). However, patients in the first phase were less likely to report rhinitis/ congestion ($p<.001$). On exam, patients in the first phase were more likely to have a higher temperature ($p=.04$) and adults ≥ 12 years were more likely to have a higher heart rate ($p<.001$).

5.2.3 Rapid influenza test results and clinical management

The proportion of rapid flu positivity was 47.3% in the first phase of the study and 37.2% in the second phase ($p=.11$). The most common clinical diagnoses by clinicians varied depending on the phase of the study. Patients in the first phase were more likely to receive a diagnosis of unspecified viral fever (45.7% versus 15.1%, $p<.001$) but less likely to receive a diagnosis of upper respiratory infection (21.2% versus 39.5%, $p=.001$) or influenza (0% versus 30.2%, $p<.001$). In addition, patients in the first phase were more likely to be prescribed an antibiotic (81.4% versus 66.3%, $p=.01$) and to have additional diagnostic tests ordered (20.6% versus 9.3%, $p=.02$). Of patients who were positive for influenza, 83.7% received a prescription for an antibiotic in the first phase, as opposed to 56.3% in the second phase ($p=.001$). Figure 8 shows the distribution of antibiotic prescriptions by month for influenza-positive and influenza-negative patients.

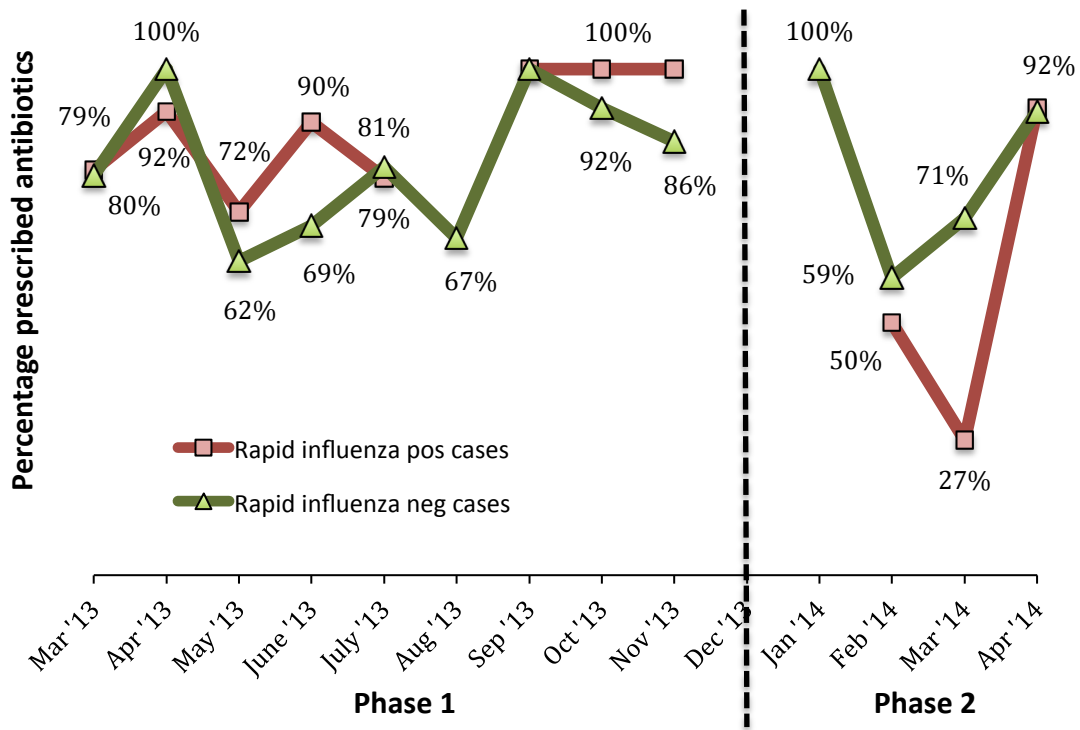


Figure 8: Percentage of rapid influenza-negative and rapid influenza-positive patients prescribed antibiotics, among outpatients with ILI in southern Sri Lanka, March 2013- April 2014.

5.3 Bivariable analysis of features associated with influenza

5.3.1 Sociodemographic characteristics, exposures, and clinical symptoms

Bivariable analysis was carried out to determine features associated with a positive rapid influenza test. No sociodemographic characteristics were associated with a positive rapid influenza test result (Table 5). Patients with influenza did not report greater expenditures on medical care, but children with a positive rapid test for influenza missed more days of school ($p=.03$), Table 6. Of exposures, having a sick

contact with similar illness was associated with 87% greater odds of influenza ($p=.003$). Several clinical symptoms were associated with influenza, including fatigue/ lethargy (OR 2.83, 95% CI 1.68- 4.86), headache (OR 2.29, 95% CI 1.38- 3.88), decreased appetite (OR 1.97, 95% CI 1.22- 3.22), myalgias (OR 2.60, 95% CI 1.60- 4.25), arthralgias (OR 2.81, 95% CI 1.73- 4.59), and pleuritic chest pain (OR 3.78, 95% CI 1.95- 7.64). On exam, patients with influenza were more likely to have a higher temperature ($p=.002$) and adults ≥ 12 years with influenza were more likely to have a higher respiratory rate ($p=.003$). Nasopharyngeal specimens were more likely to be positive than nasal specimens (OR 2.26, 95% CI 1.13- 4.73).

5.3.2 Clinical management

The associations between influenza and clinical diagnoses, antibiotic prescriptions, and ordering of diagnostic tests were analyzed separately for each phase, since clinicians in the second phase were aware of the test result (Table 7). In the first phase, a positive rapid influenza test result was not associated with any specific clinical diagnoses. In the second phase, a positive rapid influenza test result was positively associated with a clinical diagnosis of influenza ($p<.001$) and negatively associated with a clinical diagnosis of upper respiratory infection ($p<.001$). In the first phase, a positive rapid influenza test was not associated with antibiotic prescriptions or ordering of additional diagnostic tests. In the second phase, a positive rapid influenza test was

associated with lower antibiotic prescriptions ($p=.10$) and lower likelihood of ordering additional diagnostic tests ($p=.05$).

Table 5: Bivariable analysis of sociodemographic characteristics, exposures, and clinical characteristics associated with rapid influenza positivity among outpatients with ILI in southern Sri Lanka, March 2013- April 2014. Number (%) and odds ratios with 95% confidence intervals and p-values are listed for categorical variables, and medians with interquartile range and p-values using the Kruskal-Wallis test are listed for continuous variables.

	Influenza positive	Influenza negative	OR (95% CI)	p-value
Sociodemographic characteristics				
Age (years)	15.8 (8.0- 40.1)	12.5 (5.2- 37.4)		.08
Adults ≥ 12 years	106 (49.8%)	107 (50.2%)	1.42 (0.93- 2.17)	1.00
Male	103 (57.5%)	103 (48.6%)	1.43 (0.94- 2.18)	.08
Hometown				
Galle	41 (22.9%)	47 (22.2%)	1.04 (0.63- 1.73)	.86
Poddala	14 (7.8%)	28 (13.2%)	0.56 (0.26- 1.14)	.09
Akmeemana	14 (7.8%)	17 (8.0%)	0.97 (0.43- 2.17)	.94
Wanduramba	8 (4.5%)	7 (3.3%)	1.37 (0.42- 4.53)	.55
Distance to THK (km)	5.0 (3.0- 15.0)	6.0 (3.0- 15.0)		.46
Time to THK (mins)	30.0 (15.0- 45.0)	30.0 (15.0- 60.0)		.80
Occupation (adults)				
Housewife	18 (10.1%)	26 (12.3%)	0.80 (0.40- 1.58)	.49
Merchant/ shop/ office worker	17 (9.5%)	20 (9.4%)	1.01 (0.48- 2.10)	.98
Laborer/ factory worker	13 (7.3%)	13 (6.1%)	1.20 (0.50- 2.89)	.66
Farmer/ agricultural laborer	9 (5.0%)	9 (4.3%)	1.19 (0.41- 3.48)	.71
Unemployed	8 (4.5%)	10 (4.7%)	0.95 (0.32- 2.73)	.91
Educational status (patients ≥ 18 years)				
\leq O/L	57 (70.4%)	67 (69.8%)	1.03 (0.51- 2.07)	.93
\geq A/L	24 (29.6%)	28 (29.2%)	1.02 (0.51- 2.06)	.95
Exposures				

Animals				
Dogs	98 (54.8%)	120 (56.6%)	0.93 (0.61- 1.41)	.71
Cats	98 (54.8%)	106 (50.0%)	1.21 (0.80- 1.84)	.35
Mosquitoes	171 (95.5%)	205 (96.7%)	0.73 (0.22- 2.36)	.55
Birds	10 (5.6%)	10 (4.7%)	1.20 (0.43- 3.28)	.70
Smoking				
Passive	32 (17.9%)	42 (19.8%)	0.88 (0.51- 1.51)	.63
Active	14 (7.8%)	15 (7.1%)	1.11 (0.48- 2.56)	.78
Sick contact	92 (52.3%)	78 (37.0%)	1.87 (1.22- 2.86)	.003
Travel	22 (12.4%)	34 (16.0%)	0.74 (0.39- 1.36)	.30
Clinical symptoms				
1° symptom days	2 (2- 3)	2 (2- 4)		.66
Fever days	2 (1- 3)	2 (1- 3)		.93
Cough days	2 (1- 3)	2 (2- 3)		.15
Fatigue/ lethargy	152 (84.9%)	141 (66.5%)	2.83 (1.68- 4.86)	<.001
Headache	149 (83.2%)	145 (68.4%)	2.29 (1.38- 3.88)	<.001
Decreased appetite	142 (79.3%)	140 (66.0%)	1.97 (1.22- 3.22)	.004
Myalgias	144 (80.5%)	130 (61.3%)	2.60 (1.60- 4.25)	<.001
Arthralgias	144 (80.5%)	126 (59.4%)	2.81 (1.73- 4.59)	<.001
Rhinitis/ congestion	116 (64.8%)	146 (68.9%)	0.83 (0.53- 1.30)	.40
Sore throat	91 (50.8%)	94 (44.3%)	1.30 (0.85- 1.97)	.20
Shortness of breath	44 (24.6%)	39 (18.4%)	1.45 (0.86- 2.42)	.14
Vomiting	41 (22.9%)	38 (17.9%)	1.36 (0.80- 2.30)	.22
Pleuritic chest pain	40 (22.4%)	15 (7.1%)	3.78 (1.95- 7.64)	<.001
Abdominal pain	14 (7.8%)	12 (5.7%)	1.41 (0.59- 3.44)	.39
Exam findings				
Temperature (°F)	101.2 (100.7- 102)	101 (100.5- 101.7)		.002
Respiratory rate				
Adults ≥12 years	18 (16- 20)	16 (12- 20)		.003
Children <12 years	20 (18- 22)	20 (18- 22)		.39
Heart rate				
Adults ≥12 years	100 (88- 120)	96 (84- 100)		.02
Children <12 years	120 (100- 128)	100 (100- 120)		.19
Normal breath sounds	177 (98.9%)	209 (98.6%)	1.27 (0.14- 15.4)	.79
Nasopharyngeal sample	165 (92.2%)	177 (83.9%)	2.26 (1.13- 4.73)	.01

Table 6: Bivariable analysis of cost and productivity variables associated with rapid influenza positivity among outpatients with ILI in southern Sri Lanka, March 2013- April 2014. Medians with interquartile range and p-values using the Kruskal-Wallis test are listed.

	Influenza positive	Influenza negative	p-value
Rupees spent on medications	0 (0- 0)	0 (0- 0)	.61
Rupees spent on prior visits	0 (0- 0)	0 (0- 0)	.86
Rupees spent on travel for care	70 (40- 150)	72.5 (40- 150)	.73
Days of work missed (patients ≥18 yrs)	0 (0- 2)	0 (0- 1)	.45
Days of school missed (<18 yrs)	1 (0- 2)	1 (0- 1.5)	.04

Table 7: Bivariable analysis of clinical diagnoses and treatments associated with rapid influenza positivity in outpatients with ILI in southern Sri Lanka, March 2013- April 2014. Number (%) and odds ratios with 95% confidence intervals and p-values are listed. Values are reported for each phase separately.

	Influenza positive	Influenza negative	OR (95% CI)	p-value
First phase				
Clinical diagnoses				
Unspecified viral fever	65 (44.2%)	76 (47.8%)	0.87 (0.54- 1.39)	.53
Upper respiratory infection	30 (20.4%)	35 (22.0%)	0.91 (0.50- 1.63)	.73
Lower respiratory infection	20 (13.6%)	24 (15.1%)	0.89 (0.44- 1.76)	.71
Influenza	0 (0%)	0 (0%)	--	--
Antibiotic prescribed	123 (83.7%)	126 (79.3%)	1.34 (0.72- 2.52)	.32
Diagnostic test ordered	31 (21.1%)	32 (20.1%)	1.06 (0.59- 1.92)	.84
Second phase				
Clinical diagnoses				
Unspecified viral fever	2 (6.3%)	11 (20.8%)	0.25 (0.03- 1.31)	.07
Upper respiratory infection	3 (9.4%)	31 (58.5%)	0.07 (0.01- 0.29)	<.001

Lower respiratory infection	2 (6.3%)	11 (20.8%)	0.25 (0.03- 1.31)	.07
Influenza	25 (78.1%)	0 (0%)	--	<.001
Antibiotic prescribed	18 (56.3%)	39 (73.6%)	0.46 (0.17- 1.29)	.10
Diagnostic test ordered	5 (15.6%)	2 (3.8%)	4.72 (0.70- 51.7)	.05

5.4 Bivariable analysis of features associated with antibiotic prescriptions

5.4.1 Sociodemographic characteristics, exposures, and clinical symptoms

Bivariable analysis was carried out to determine features associated with receipt of an antibiotic prescription. No sociodemographic characteristics were associated with antibiotic prescription (Table 8). Patients who were prescribed antibiotics had spent more on medications for the same illness ($p=.02$) and on prior medical visits for the same illness ($p=.03$), Table 9. Adults ≥ 18 years who received an antibiotic prescription had missed more days of work ($p=.04$). No sick contact, animal, or travel exposures were significantly associated with receipt of an antibiotic prescription. Of clinical symptoms, only fatigue was associated with a greater likelihood of antibiotic prescriptions (OR 1.71, 95% CI 0.98- 2.96). On exam, a higher heart rate was associated with a greater likelihood of antibiotic prescription among children <12 years ($p<.001$).

5.4.2 Clinical management

The associations between antibiotic prescriptions and clinical diagnoses and ordering of diagnostic tests were analyzed separately for each phase, since clinicians in

the second phase were aware of the test result (Table 10). In the first phase, a clinical diagnosis of unspecified viral fever was associated with fewer antibiotic prescriptions ($p < .001$), while a clinical diagnosis of upper respiratory infection was associated with a higher proportion of antibiotic prescriptions ($p = .003$). In the first phase, antibiotic prescriptions were not associated with rapid influenza test results, but patients who received an antibiotic prescription were more likely to have an additional diagnostic test such as full blood count ordered ($p = .03$). In the second phase, patients with a clinical diagnosis of lower respiratory infection were more likely to receive an antibiotic prescription ($p = .005$). In addition, a smaller proportion of patients with a positive rapid influenza test or a clinical diagnosis of influenza were prescribed an antibiotic, but this was not statistically significant, possibly because of small sample size ($p = .10$ and $p = .11$, respectively). There was no correlation between antibiotic prescriptions and diagnostic tests ordered, but the overall number of tests ordered in the second phase was low.

Table 8: Bivariable analysis of sociodemographic characteristics and clinical features associated with antibiotic prescriptions for outpatients with ILI in southern Sri Lanka, March 2013- April 2014. Number (%) and odds ratios with 95% confidence intervals and p-values are listed for categorical variables, and medians with interquartile range and p-values using the Kruskal-Wallis test are listed for continuous variables. Values are reported for the entire study population.

	Antibiotic prescribed	No antibiotic prescribed	OR (95% CI)	p-value
Sociodemographic characteristics				
Age (years)	14.0 (6.1- 37.4)	12.9 (5.7- 40.7)		.92
Adults ≥18 years	139 (44.8%)	41 (47.1%)	0.91 (0.55- 1.51)	.71
Male	169 (54.5%)	40 (46.0%)	1.41 (0.85- 2.34)	.16
Hometown				
Galle	72 (23.2%)	19 (21.8%)	1.08 (0.60- 2.04)	.79
Poddala	33 (10.7%)	9 (10.3%)	1.03 (0.46- 2.56)	.94
Akmeemana	25 (8.1%)	6 (6.9%)	1.18 (0.45- 3.65)	.72
Wanduramba	11 (3.6%)	4 (4.6%)	0.76 (0.22- 3.37)	.65
Distance to THK (km)	5.0 (3.0- 15.0)	8.0 (3.0- 15.0)		.83
Time to THK (minutes)	30 (15- 60)	30 (15- 30)		.27
Occupation (adults)				
Housewife	31 (22.3%)	14 (34.2%)	0.55 (0.25- 1.29)	.12
Merchant/ shop/ office worker	30 (21.6%)	4 (9.8%)	2.55 (0.81- 10.6)	.09
Laborer/ factory worker	22 (15.8%)	3 (7.3%)	2.38 (0.66- 13.1)	.17
Farmer/ agricultural laborer	12 (8.6%)	6 (14.6%)	0.55 (0.18- 1.93)	.26
Unemployed	10 (7.2%)	6 (14.6%)	0.45 (0.14- 1.63)	.14
Educational status (adults)				
≤ O/L	95 (68.4%)	30 (73.2%)	0.79 (0.33- 1.81)	.56
≥ A/L	43 (30.9%)	11 (26.8%)	1.22 (0.53- 2.96)	.61
Exposures				
Animals				
Dogs	172 (55.5%)	49 (56.3%)	0.97 (0.58- 1.60)	.89
Cats	166 (53.6%)	42 (48.3%)	1.24 (0.75- 2.05)	.38

Mosquitoes	298 (96.1%)	84 (96.6%)	0.89 (0.16- 3.39)	.86
Birds	16 (5.2%)	4 (4.6%)	1.13 (0.35- 4.77)	.83
Smoking				
Passive	53 (17.1%)	21 (24.1%)	0.65 (0.36- 1.22)	.14
Active	26 (8.4%)	3 (3.5%)	2.56 (0.76- 13.5)	.12
Sick contact	128 (41.8%)	44 (50.6%)	0.70 (0.42- 1.17)	.15
Travel	50 (16.2%)	7 (8.1%)	2.21 (0.94- 5.99)	.06
Clinical symptoms				
1° symptom days	2 (2- 4)	2 (2- 3)		1.00
Fever days	2 (1- 3)	2 (1- 3)		.19
Cough days	2 (2- 3)	2 (1- 3)		.46
Fatigue/ lethargy	240 (77.4%)	58 (66.7%)	1.71 (0.98- 2.96)	.04
Headache	238 (76.8%)	60 (69.0%)	1.49 (0.84- 2.58)	.14
Decreased appetite	228 (73.6%)	57 (65.5%)	1.46 (0.85- 2.50)	.14
Myalgias	220 (71.0%)	57 (65.5%)	1.29 (0.75- 2.19)	.33
Arthralgias	217 (70.0%)	55 (63.2%)	1.36 (0.79- 2.29)	.23
Rhinitis/ congestion	205 (66.1%)	60 (69.0%)	0.88 (0.51- 1.50)	.62
Sore throat	153 (49.4%)	34 (39.1%)	1.52 (0.91- 2.55)	.09
Shortness of breath	71 (22.9%)	14 (16.1%)	1.55 (0.81- 3.15)	.17
Vomiting	65 (21.0%)	14 (16.1%)	1.38 (0.72- 2.83)	.31
Pleuritic chest pain	45 (14.5%)	10 (11.5%)	1.31 (0.61- 3.05)	.47
Abdominal pain	22 (7.1%)	5 (5.8%)	1.25 (0.44- 4.36)	.66
Exam findings				
Temperature (°F)	101.1 (100.6- 101.9)	101 (100.5- 101.7)		.24
Respiratory rate				
Adults ≥12 years	18 (14- 20)	18 (12- 20)		.81
Children ≤12 years				
Heart rate				
Adults ≥12 years	100 (88- 112)	96 (88- 112)		.85
Children <12 years	120 (100- 128)	100 (92- 120)		<.001
Normal breath	307 (99.0%)	85 (97.7%)	2.41 (0.20- 21.3)	.33
Sounds				

Table 9: Bivariable analysis of cost and productivity variables associated with antibiotic prescriptions for outpatients with ILI in southern Sri Lanka, March 2013- April 2014. Medians with interquartile range and p-values using the Kruskal-Wallis test are listed. Values are reported for the entire study population.

	Influenza positive	Influenza negative	p-value
Rupees spent on medications	0 (0- 0)	0 (0- 0)	.02
Rupees spent on prior visits	0 (0- 0)	0 (0- 0)	.03
Rupees spent on travel for care	70 (40- 120)	100 (40- 200)	.23
Days of work missed (adults ≥18 yrs)	0 (0- 2)	0 (0- 1)	.04
Days of school missed (<18 yrs)	1 (0- 2)	1 (0- 1)	.75

Table 10: Bivariable analysis of clinical diagnoses and treatments associated with antibiotic prescriptions for outpatients with ILI in southern Sri Lanka, March 2013- April 2014. Number (%) and odds ratios with 95% confidence intervals and p-values are listed. Values are reported for each phase separately.

	Antibiotic prescribed	No antibiotic prescribed	OR (95% CI)	p-value
First phase				
Clinical diagnoses				
Unspecified viral fever	100 (39.5%)	42 (72.4%)	0.25 (0.12- 0.48)	<.001
Upper respiratory infection	62 (24.5%)	4 (6.9%)	4.38 (1.52- 17.3)	.003
Lower respiratory infection	40 (15.8%)	5 (8.6%)	1.99 (0.73- 6.76)	.16
Influenza	0 (0%)	0 (0%)	--	--
Rapid flu positive	123 (49.4%)	24 (42.1%)	1.34 (0.72- 2.52)	.32
Diagnostic test Ordered	58 (22.9%)	6 (10.3%)	2.58 (1.03- 7.70)	.03
Second phase				
Clinical diagnoses				
Unspecified viral Fever	7 (12.3%)	6 (20.7%)	0.54 (0.14- 2.18)	.30
Upper respiratory Infection	23 (40.4%)	11 (37.9%)	1.11 (0.40- 3.10)	.83
Lower respiratory Infection	13 (22.8%)	0 (0%)	--	.005

Influenza	14 (24.6%)	12 (41.4%)	0.46 (0.16- 1.34)	.11
Rapid flu positive	18 (31.6%)	14 (50.0%)	0.46 (0.17- 1.29)	.10
Diagnostic test Ordered	5 (8.8%)	3 (10.3%)	0.83 (0.15- 5.79)	.81

5.5 Multivariable analysis of features associated with influenza

Multivariable logistic regression was carried out to determine features associated with rapid influenza positivity. Age, sex, and any sociodemographic characteristics, exposures, clinical symptoms, or exam findings that were significant at the 0.10 level on bivariable analysis for either adults or children were included in the model (Table 11). On multivariable analysis, male sex (OR 1.70, 95% CI 1.08- 2.69), history of a sick contact (OR 1.87, 95% CI 1.19- 2.96), pleuritic chest pain (OR 2.76, 95% CI 1.36- 5.59), a higher temperature (OR 1.43, 95% CI 1.09- 1.86), and having a sample obtained from the nasopharynx (OR 2.14, 95% CI 1.01- 4.55) were associated with rapid influenza test positivity.

Table 11: Multivariable analysis of sociodemographic characteristics, exposures, clinical symptoms, and exam findings associated with rapid influenza positivity among outpatients with ILI in southern Sri Lanka, March 2013- April 2014. A generalized linear model with logistic regression was carried out, and odds ratios with 95% confidence intervals and p-values are listed.

	OR (95% CI)	p-value
Age	1.00 (0.99- 1.01)	.96
Male sex	1.70 (1.08- 2.69)	.02
Hometown- Poddala	0.53 (0.25- 1.11)	.09
Sick contact	1.87 (1.19- 2.96)	.01
Fatigue	1.43 (0.76- 2.68)	.27
Headache	1.27 (0.71- 2.28)	.42
Decreased appetite	1.18 (0.69- 2.04)	.55
Myalgias	0.32 (0.03- 2.99)	.32
Arthralgias	5.29 (0.58- 48.4)	.14
Pain with breathing	2.76 (1.36- 5.59)	.01
Temperature (°F)	1.43 (1.09- 1.86)	.01
Respiratory rate	1.01 (0.97- 1.06)	.52
Heart rate	1.01 (0.99- 1.02)	.44
Nasopharyngeal sample	2.14 (1.01- 4.55)	.05

5.6 Multivariable analysis of features associated with receipt of an antibiotic prescription

Multivariable logistic regression was carried out to determine features associated with receipt of an antibiotic prescription. Age, sex, rapid influenza test result, and any sociodemographic characteristics, exposures, clinical symptoms, exam findings, or clinical care variables that were significant at the .05 level on bivariable analysis of the entire study population were included in the model (Table 12). In addition, clinical diagnoses and any diagnostic testing received, if significant at the .05 level on bivariable analysis of each phase, were included separately for each phase since these variables

may have been affected by knowledge of the rapid influenza test result. For phase 1, being of male sex (OR 1.94, 95% CI 1.01- 3.72) and having a diagnosis other than unspecified viral fever (OR 0.87, 95% CI 0.80- 0.94) were associated with antibiotic prescriptions. For phase 2, the clinical symptom of fatigue (OR 10.8, 95% CI 2. 5- 46.2) and having a negative rapid influenza test result (OR 0.20, 95% CI 0.05- 0.85) were associated with receipt of antibiotic prescriptions.

Table 12: Multivariable analysis of sociodemographic characteristics, exposures, clinical symptoms, and exam findings associated with antibiotic prescriptions among outpatients with ILI in southern Sri Lanka, March 2013- April 2014. A generalized linear model with logistic regression was carried out separately for each phase. Odds ratios with 95% confidence intervals and p-values are listed.

	Phase 1		Phase 2	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age	0.99 (0.97- 1.00)	.09	1.03 (0.99- 1.06)	.13
Male sex	1.94 (1.01- 3.72)	.04	1.25 (0.39- 3.99)	.71
Rupees spent on prior medications	1.01 (0.99- 1.01)	.17	0.99 (0.96- 1.01)	.28
Rupees spent on prior visits	0.99 (0.98- 1.01)	.48	1.02 (0.98- 1.06)	.35
Fatigue	0.69 (0.30- 1.59)	.39	10.8 (2.5- 46.2)	.001
Diagnosis- unspecified viral fever	0.87 (0.80- 0.94)	<.001	--	--
Diagnosis- upper resp infection	1.07 (0.95- 1.21)	.29	--	--
Diagnosis- lower resp infection	--	--	7.17 (2.1x10 ⁻⁴ - 2.4x10 ⁵)	.99
Diagnostic test ordered	2.21 (0.82- 5.97)	.12	--	--
Positive rapid influenza test	1.30 (0.68- 2.48)	.42	0.20 (0.05- 0.85)	.03

6. Discussion

Acute febrile respiratory illnesses, including ILI, are an important cause of unnecessary antibiotic prescriptions. In this public, tertiary care hospital in southern Sri Lanka, approximately 1% of patients presenting to the outpatient department from March 2013- April 2014 had ILI. Half of ILI cases were due to influenza virus, with most of these patients having influenza A. Antibiotics were prescribed for the majority of patients with ILI, with male sex and having the clinical symptom of fatigue being associated with receiving antibiotic prescriptions. Access to rapid influenza test results was associated with decreased antibiotic prescriptions in the second phase of the study, but further work is necessary to determine if this effect is sustained.

6.1 ILI and influenza patterns in southern Sri Lanka

The proportion of outpatients with influenza was high in this study, accounting for almost 50% of ILI cases. During the large peak in influenza activity observed from March- July 2013, influenza B accounted for approximately one-third of cases, which may be higher than expected during an epidemic. However, the pattern of influenza B in Sri Lanka has not been well characterized, and case studies indicate that the virus causes

significant disease and small outbreaks in the country.¹ The peak in influenza coincided with the first rainy season in the southern region of the country, and ongoing lower levels of influenza activity from September- November 2013 coincided with the second rainy season. Since the influenza epidemic documented in our study occurred during the rainy season associated with less rainfall, the true association between weather patterns and influenza in southern Sri Lanka remains unclear.

Data regarding seasonal influenza patterns from lower-income settings in tropical and subtropical settings are lacking, although global surveillance of influenza has increased considerably since the emergence of H5N1 avian influenza in 2003 and the pandemic of H1N1 influenza in 2009. Available data indicate that countries in tropical regions can experience annual epidemics coinciding with the local rainy season, semi-annual epidemics, or year-round influenza activity. A recent analysis by Tamerius *et al* showed that of 78 sites worldwide, sites with low levels of specific humidity and temperature for at least one month during the year were characterized by seasonal influenza activity during these months, while sites that maintained high levels of specific humidity and temperature year-round were characterized by influenza

¹ Abeysekera, R. A., Imbulpitiya, I. V. B., Ponnampereuma, S., & Kularatne, S. A. M. (2013). Influenza B infection, an underestimated killer– an experience at a Tertiary care Hospital– Sri Lanka. *Sri Lankan Journal of Infectious Diseases*, 3(1), 40–44.

epidemics during the most humid and rainy months of the year.² A review of data from the World Health Organization's FluNet database, which captures worldwide data on influenza viruses by subtype, shows that the peak influenza period in Sri Lanka has varied annually over the last few years.³ Recent peaks appear to have occurred from October 2010- February 2011, June 2011- July 2011, September 2011- March 2012, May 2012- January 2013, and April 2013- June 2013. The FluNet data reflect specimens received from the entire country, and do not characterize specific patterns of influenza from the Southern Province. Further studies correlating rates of influenza with temperature, humidity, rainfall, and social patterns are needed to better describe the epidemiology of influenza in southern Sri Lanka.

In our study, no patients reported having ever received the influenza vaccine. In higher-income settings, influenza vaccination has been shown to be cost-effective, but no data exist from low and lower-middle income countries.⁴ Influenza vaccination rates remain low in Sri Lanka, and the vaccine is only provided through the private sector.⁵

² Tamerius, J. D., Shaman, J., Alonso, W. J., Bloom-feshbach, K., Uejio, C. K., & Comrie, A. (2013). Environmental Predictors of Seasonal Influenza Epidemics across Temperate and Tropical Climates. *PLoS Pathogens*, 9(3).

³ World Health Organization. (2014). FluNet. Retrieved May 31, 2014, from http://www.who.int/influenza/gisrs_laboratory/flunet/en/

⁴ Peasah, S. K., Azziz-Baumgartner, E., Breese, J., Meltzer, M. I., & Widdowson, M.-A. (2013). Influenza cost and cost-effectiveness studies globally--a review. *Vaccine*, 31(46), 5339-48.

⁵ Attygalle, R. (2013, July 13). Getting vaccinated the proper way. *The Island*. Colombo.

A better understanding of the patterns of influenza activity in Sri Lanka may help direct timed risk communication messages and influenza vaccination efforts in the country.

The percentage of ILI in this study of outpatients in southern Sri Lanka ranged from 0.3% to 1.8% of surveyed patients from March 2013 to April 2014, with rates peaking in March- June 2013 in concert with the rise in influenza activity. No published data regarding ILI patterns in Sri Lanka are available for comparison. The largest category of patients with ILI was in the 5-10 year age range followed by the <5 years age range, which is consistent with data from other studies showing that children <17 years have the highest incidence of influenza virus-associated clinic visits.⁶ Confirmed influenza activity was lower during the second phase of this study, with results trending towards significance, suggesting a changing epidemiology of ILI with time. This was associated with a changing pattern in clinical symptoms, with patients in the first phase having a higher likelihood of symptoms such as fatigue, malaise, and headache, while patients in the second phase reporting more rhinitis and congestion. Discovering the

⁶ Fowlkes, A., Giorgi, A., Erdman, D., Temte, J., Goodin, K., Di Lonardo, S., ... Finelli, L. (2014). Viruses Associated With Acute Respiratory Infections and Influenza-like Illness Among Outpatients From the Influenza Incidence Surveillance Project, 2010-2011. *The Journal of Infectious Diseases*, 209, 1715– 1725.

etiology of illness in these rapid influenza-negative patients is important for informing public health efforts in the country.

6.2 Clinical presentation of influenza

On multivariable analysis, being of male sex, having a sick contact, having pain on breathing, having a higher temperature, and using a nasopharyngeal versus nasal specimen were all associated with a positive rapid test for influenza. These characteristics have been linked with influenza in other studies. Tan *et al* showed that a higher temperature was associated with influenza virus versus other causes of acute febrile respiratory illness.⁷ Limited studies from developed countries such as the US and Spain indicate that the reported incidence of influenza is higher in males than in females, in age groups ranging from infants to elderly adults.⁸ Pleuritic chest pain has been described in patients with influenza, although this has been seen more with the pandemic strain than with seasonal influenza.⁹ All these features may be helpful in identifying patients with influenza, but the non-specific nature of these characteristics

⁷ Tan, X. Q., Zhao, X., Lee, V. J., Loh, J. P., Tan, B. H., Koh, W. H., ... Cook, A. R. (2014). Respiratory viral pathogens among Singapore military servicemen 2009 – 2012: epidemiology and clinical characteristics. *BMC infectious diseases*, 14(1), 204.

⁸ World Health Organization. (2010). *Sex, gender and influenza*.

⁹ Shiley, K., Nadolski, G., Mickus, T., Fishman, O., & Lautenbach, E. (2011). Differences in the epidemiological characteristics and clinical outcomes of pandemic (H1N1) 2009 influenza, compared with seasonal influenza. *Infect Control Hosp Epidemiol*, 31(7), 676–682.

highlights the reason that diagnostic testing may be important in such populations. In developing settings, the importance of rapid diagnostics for viral infections such as influenza may be in reducing antibiotic use and informing infection control and public health efforts, rather than in directing antiviral use. In otherwise healthy patients, while treatment with neuraminidase inhibitors can reduce the time to first alleviation of symptoms by 17 hours in adults and 29 hours in children, there appears to be no benefit in reducing hospitalizations, severe influenza complications, or radiologically confirmed pneumonia.¹⁰

6.3 ILI and antibiotic use

In this pretest-posttest study of outpatients with ILI in Southern Sri Lanka, 80% of patients received a prescription for an antibiotic at baseline. There was a significant decrease in the proportion of patients prescribed antibiotics and in whom additional diagnostic tests were recommended between the two phases of the study. Multivariable analysis of patients in the second phase showed that a positive influenza test was associated with 80% lower odds of receiving an antibiotic prescription, which suggests that the provision of the rapid influenza test result may have been important in this reduction. In addition, comparison of influenza-positive patients between the first and

¹⁰ Jefferson, T., Ma, J., Doshi, P., Cb, D. M., Hama, R., Mj, T., ... Cj, H. (2014). Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children (Review). *Cochrane Database Syst Rev*, Apr 10(4).

second phases showed a relative decrease of almost 30% in antibiotic prescriptions, further suggesting that knowledge of the test result may have been pivotal in clinicians' decision-making processes.

Our finding of high baseline frequency of antibiotic prescriptions for outpatients with ILI mirrors frequencies seen throughout the developed and developing worlds. In the United States, patients presenting with acute respiratory tract infections such as bronchitis and rhinitis receive a prescription for an antibiotic during 50% of ambulatory care visits and 61% of Emergency Department (ED) visits.¹¹ An analysis of primary care visits in Southeast Asia between 1990 and 2006 showed that more than 50% of upper respiratory tract infections were treated with antibiotics, while only 53% of pneumonias were treated with appropriate antibiotics.¹² In a rural province in Eastern Thailand, 82% of outpatients with ILI received a prescription for an antibiotic during a study conducted in 2003- 2004.¹³ Data from Sri Lanka are lacking, but Lucas *et al.* showed that

¹¹ Donnelly, J. P., Baddley, J. W., & Wang, H. E. (2014). Antibiotic utilization for acute respiratory tract infections in U.S. emergency departments. *Antimicrobial Agents and Chemotherapy*, 58(3), 1451–7.

¹² World Health Organization. (2009). *Medicines use in primary care in developing and transitional countries*.

¹³ Bhavnani, D., Phatinawin, L., Chantira, S., Olsen, S. J., & Simmerman, J. M. (2007). The Influence of Rapid Influenza Diagnostic Testing on Antibiotic Prescribing Patterns in Rural Thailand. *International Journal of Infectious Diseases*, 11(4), 355–9.

47% of patients with acute respiratory infection admitted to the largest public pediatric hospital in the country may have been treated unnecessarily with antibiotics.¹⁴

The relatively higher baseline proportion of antibiotic prescriptions in this study is likely secondary to a multitude of factors including short patient-provider interaction times due to the high volume of patients, lack of routine access to diagnostic tests for pathogens as influenza and Streptococcus, and potential patient expectations for a medication prescription. One study of outpatient care visits in the US from 1995 to 2000 showed that patients receiving antibiotics had shorter visit times (14.2 minutes versus 15.2 minutes).¹⁵ In the busy OPD of this hospital in Sri Lanka, where typically more than 1000 patients are seen daily and individual patient visits tend to last less than 5 minutes, there is likely little time for clinicians to engage in rational decision-making. Diagnostic test results, which are important for providing clinicians with feedback regarding their decision-making and in improving the specificity of their treatment, are lacking in this setting; the fact that 40% of patients in this study were diagnosed with unspecified viral fever highlights this fact. Patients' expectations and providers' perceptions of those expectations may also play a role in the prescription of antibiotics. One study from Hong

¹⁴ Lucas, M. N., Liyanage, U. A., & Lokukankanamage, L. K. U. I. (2001). A study of antibiotic usage in acute respiratory infections in children. *Sri Lankan Journal of Child Health*, 7, 5-7.

¹⁵ Linder, J. a, Singer, D. E., & Stafford, R. S. (2003). Association between antibiotic prescribing and visit duration in adults with upper respiratory tract infections. *Clinical therapeutics*, 25(9), 2419-30.

Kong showed that patient satisfaction and the belief that patients who wanted antibiotics would obtain them anyway were the most common reasons given by family physicians who self-identified themselves as over-prescribing antibiotics for ARTIs.¹⁶ Studies from the US indicate that between 60 and 75% of patients with upper respiratory tract infections perceive a need for an antibiotic. However, patient satisfaction appeared to be related to patients' perception of care received and whether the diagnosis and treatment were explained, rather than whether they received an antibiotic.¹⁷ The feasibility and effectiveness of pursuing such a comprehensive care approach in this setting in Sri Lanka have not been explored. In our study, the educational status of patients was relatively low, and only 4.5% of patients reported receiving a prior antibiotic; however, 17.2% of patients were unsure about the receipt of an antibiotic. This suggests that patients' expectations may be for a medication prescription or intervention, rather than specifically for an antibiotic prescription. Finally, the absence of medical records in this outpatient setting, the lack of continuity of care in the OPD, and

¹⁶ Lam, T. P., & Lam, K. F. (2003). What are the non-biomedical reasons which make family doctors over-prescribe antibiotics for upper respiratory tract infection in a mixed private/ public Asian setting? *Journal of Clinical Pharmacy and Therapeutics*, 28(3), 197–201.

¹⁷ Linder, J. a, Singer, D. E., & Stafford, R. S. (2003). Association between antibiotic prescribing and visit duration in adults with upper respiratory tract infections. *Clinical therapeutics*, 25(9), 2419–30.

the provision of antibiotics free of charge through public hospitals may also play a role in the high frequency of antibiotic prescriptions seen in our study.

The drop in antibiotic prescriptions associated with and potentially caused by providing rapid influenza test results is encouraging, and is in keeping with results from other studies in the developed world. A retrospective observational study of children presenting to a US ED with acute respiratory symptoms revealed that children who tested positive using a rapid influenza test were significantly less likely to receive antibiotics than children who tested negative (20% versus 53%).¹⁸ Another US study of hospitalized adults with cardiopulmonary disease, who tested positive for influenza by either PCR or serology, showed that patients who had a positive influenza antigen test were significantly less likely to receive antibiotics (86% versus 99%).¹⁹ Several randomized controlled trials of pediatric patients in the developed world have also shown that access to rapid influenza testing can reduce antibiotic use. Bonner *et al.* showed that ED physicians' knowledge of the rapid influenza test result was associated with lower antibiotic use in influenza-positive children (7.3% versus 24.5%), fewer

¹⁸ Noyola, D. E., & Demmler, G. J. (2000). Effect of Rapid Diagnosis on Management of Influenza A infections. *The Pediatric Infectious Disease Journal*, 19(4), 303–307.

¹⁹ Falsey, A. R., Murata, Y., & Walsh, E. E. (2007). Impact of Rapid Diagnosis on Management of Adults Hospitalized With Influenza. *Archives of Internal Medicine*, 167, 354–360.

diagnostic tests ordered, and shorter length of stay in the ED.²⁰ Esposito *et al.* showed that children with a positive rapid influenza test were less likely to receive antibiotics (32.6% versus 64.8%) and undergo routine blood work in an Italian ED.²¹ However, only one published study to date has studied the use of rapid tests in less developed settings, where antibiotic use is generally more prevalent and less regulated. A retrospective analysis of outpatients presenting with ILI to five outpatient departments in Thailand showed that patients who tested positive for influenza were less likely to be prescribed antibiotics than patients who tested negative (73% versus 87%).²²

Our results imply that access to and use of rapid diagnostic testing such as for influenza may have a significant impact on decreasing inappropriate antibiotic prescriptions. However, solely providing access to such testing is likely not adequate. Fifty-six percent of patients who tested positive for influenza in the second phase of our study still received antibiotics, as opposed to 74% of those who were negative for influenza in the second phase. In addition, in patients positive for influenza in the

²⁰ Bonner, A. B., Monroe, K. W., Talley, L. I., Klasner, A. E., & Kimberlin, D. W. (2003). Impact of the Rapid Diagnosis of Influenza on Physician Decision-Making and Patient Management in the Pediatric Emergency Department: Results of a Randomized, Prospective, Controlled Trial. *Pediatrics*, *112*, 363–367.

²¹ Esposito, S., Marchisio, P., Morelli, P., Crovari, P., & Principi, N. (2003). Effect of a Rapid Influenza Diagnosis. *Archives of Disease in Childhood*, *88*(6), 525–6.

²² Bhavnani, D., Phatinawin, L., Chantra, S., Olsen, S. J., & Simmerman, J. M. (2007). The Influence of Rapid Influenza Diagnostic Testing on Antibiotic Prescribing Patterns in Rural Thailand. *International Journal of Infectious Diseases*, *11*(4), 355–9.

second phase, the proportion receiving antibiotics dropped to 50% in the first month, followed by 27% in the second month. However, the proportion rose to 93% by the third month. This suggests that the impact of providing such test results may be short-lived, unless there is continuous education and reinforcement regarding the importance of decreasing unnecessary antibiotic use. An informational session was conducted with physicians in the OPD prior to the second phase of our study, but this was not repeated. The introduction of new staff who may not understand the implications of a rapid influenza test result may also have played a role in the rising number of antibiotic prescriptions. Interestingly, in the first phase, multivariable analysis showed that male sex was associated with greater odds of receiving an antibiotic prescription. A prior study in the US showed that male Medicaid recipients with ARTIs were more likely to receive antibiotic prescriptions than female recipients; the reason for this was not obvious.²³ In the relatively patriarchal setting in Sri Lanka, it is possible that male patients' expectations for antibiotic treatment are higher or that physicians' beliefs regarding the severity of illness in men versus women are different. However, this needs to be explored further.

²³ Brown, D. W., Taylor, R., Rogers, A., Weiser, R., & Kelley, M. (2003). Antibiotic Prescriptions Associated with Outpatient Visits for Acute Upper Respiratory Tract Infections among Adult Medicaid Recipients in North Carolina. *NC Med J*, 64(4).

Studies from other settings indicate that a multi-faceted approach is required for a problem as complex as over-prescription of antibiotics. A WHO analysis of 121 interventions in 82 well-designed studies to improve antibiotic use for conditions such as diarrhea or respiratory tract infections from 1990 to 2006 showed that provider education or distribution of printed materials alone had little impact on medication use, while multi-faceted interventions involving education of both prescribers and consumers in conjunction with supervision improved use by 20-30%.²⁴ In the US, the proportion of ambulatory ARTI visits resulting in antibiotics dropped from 65% to 50% over the course of 1995 to 2006. This has been attributed to multiple efforts including the Campaign for Appropriate Antibiotic Use in the Community launched by the Centers for Disease Control and Prevention in 1995, which led to the publication of “The Principles” for appropriate antibiotic use for pediatric upper respiratory tract infections.²⁵ This program was renamed the “Get Smart: Know When Antibiotics Work” in 2003 as part of a national media campaign, with the goal of reducing antimicrobial resistance by promoting adherence to prescribing guidelines by clinicians, decreasing unnecessary demand for antibiotics from the community, and increasing adherence to

²⁴ Holloway, K. A. (2011). Promoting the rational use of antibiotics. *Regional Health Forum*, 15(1), 122–130.

²⁵ Grijalva, C. G., Griffin, M. R., & Page, P. (2014). Antibiotic Prescription Rates for Acute Respiratory Tract Infections in US Ambulatory Settings. *JAMA*, 302(7), 758–766.

prescribed antibiotics.²⁶ In the United Kingdom, the National Institute for Health and Care Excellence recommends a strategy of either no antibiotics or delayed antibiotic prescribing for treating acute uncomplicated respiratory tract infections. A recent randomized controlled trial comparing no antibiotic use with delayed antibiotic use (recontact for prescription, post-dated prescription, collection of prescription, or patient-led prescriptions) showed that delayed prescriptions resulted in fewer than 40% of patients receiving antibiotics, with no difference in symptom scores, patient satisfaction, or patients' belief in antibiotics.²⁷

In this developing world setting, a multi-faceted approach that focuses on prescriber interventions (improved diagnostics, guideline use, feedback), consumer interventions (education), and regulatory interventions (controlling access in both inpatient and outpatient settings) will likely be necessary.²⁸ The Sri Lanka Medical Association (SLMA), which is the national professional medical association in the country, published guidelines on the appropriate use of antimicrobial agents for a spectrum of infectious conditions in 2012.²⁹ However, concerted efforts from the

²⁶ Centers for Disease Control and Prevention. (2013b). Get smart: know when antibiotics work. Retrieved May 30, 2014, from <http://www.cdc.gov/getsmart/campaign-materials/about-campaign.html>

²⁷ Moore, M., Kelly, J., & Williamson, I. (2014). Delayed antibiotic prescribing strategies for respiratory tract infections in primary care: pragmatic, factorial, randomised controlled trial. *BMJ*, 1606(March), 1–8.

²⁸ Christiansen, K., Carbon, C., & Cars, O. (2002). Moving from recommendation to implementation and audit: Part 2. Review of interventions and audit. *Clinical microbiology and infection*, 8(Suppl 2), 107–28.

²⁹ Sri Lanka Medical Association. (2012). *SLMA Guidelines on the Use of Antimicrobial Agents*. Colombo.

Ministry of Health, professional medical societies, and the lay community in Sri Lanka are likely necessary to make an impact on the growing problem of antibiotic overuse and antimicrobial resistance.

7. Ongoing work

In order to reach the pre-determined sample size for establishing whether access to rapid influenza test results is associated with reduced antibiotic prescriptions, study enrollment into the second phase of the study is ongoing. Enrollment is expected to be complete by December 2014. In addition to providing information about antibiotic use, these data would provide further information regarding the patterns of influenza over time in southern Sri Lanka.

The PCR testing of samples stored at -70°C is expected to be completed by December 2014, and will include testing for influenza as well as other respiratory viruses. The results from this testing will confirm influenza infections and identify non-influenza etiologies of ILI in southern Sri Lanka, and may help inform public health efforts. In addition, such testing will allow the test performance characteristics of this rapid influenza test to be described, and will help validate the test in the Sri Lankan population.

The second phase of the study included a follow-up telephone survey 1-2 weeks after the patient's OPD visit in order to describe symptom resolution, further care or medications received, impact of the illness on finances and productivity, and possible adverse effects related to antibiotic use. The collection of data from these follow-up encounters will be completed by December 2014.

8. Conclusions

Influenza is an important cause of acute respiratory infections among outpatients in southern Sri Lanka, and is associated with high antibiotic use. On multivariable analysis, the proportion of patients receiving antibiotics was lower among influenza-positive patients when results were available to clinicians, suggesting that access to such testing may help reduce unnecessary antibiotic use. However, a multi-faceted approach consisting of provider interventions, patient education, and regulatory measures is likely necessary for a meaningful and sustained impact on indiscriminate antibiotic use. Identifying methods to promote the rational use of antibiotics in all settings is urgent given the growing worldwide threat of antimicrobial resistance.

Appendix A

Structured questionnaire administered to patients.

OUPATIENT FEBRILE RESPIRATORY ILLNESS STUDY
FLU ID _____ DATE __/__/__(DD/MM/YR) SEEN/EXAM BY (INITIALS): ____
THK HOSPITAL, SRI LANKA REVIEWED BY: DATA ENTRY:

IDENTIFYING INFORMATION: CONFIDENTIAL FACE SHEET

1. Patient name (Last): _____
2. Patient name (First): _____
3. Hospital ID
(OPD # or BHT #): _____
4. DOB __/__/____
5. Occupation: _____
6. Consent given by:
 self (Patient = >18 yrs)
 other (caregiver, <18 yrs)
If other, name (Last, first): _____
7. Assent given? (child >12 yrs and developmentally normal)
 yes no
8. Patient's home /postal address: _____

9. Patient's primary residence (where spend most time): _____

10. Patient/family telephone number: _____ mobile _____
 patient's home other (specify: relation/friend) _____
Other contact info: _____ school work

OUPATIENT FEBRILE RESPIRATORY ILLNESS STUDY

FLU ID _____ DATE ___/___/___ (DD/MM/YR) SEEN/EXAM BY (INITIALS): _____
 THK HOSPITAL, SRI LANKA REVIEWED BY: _____ DATA ENTRY: _____

BACKGROUND/EPIDEMIOLOGY

Age ___ yr ___ mo Sex "M" "F"
 Date of visit: ___/___/___

Sick contact with similar illness in past ___ weeks

"No" "in house" "at work or school" "other" _____

Prior visit for same illness "Yes" "No"

"GP" "OPD" "Other" _____

Travel in last 30 days date: ___/___/___

"No" "Provincial" "Sri Lankan" "International"

"Unsure" Describe _____

Work (check for patient-circle for HOH if age <18)

"housewife" "unemployed" "retired"

"school (teacher, student)" "military/police/security"

"farmer or laborer, agricultural" "laborer, factory"

"merchant/ shop/office worker"

"construction worker" "other" _____

Education (check for patient-circle for HOH if

<18) "<O/L" "O/L" "A/L" ">A/L"

Residence Distance(km) from THK _____

Time to THK _____ GS _____

Exposure to animals in/around home

"Dog" "Cat" "Pig" "Cow" "Rodent"

"Goat" "Birds" "Mosquito" "Other" _____

Exposure to tobacco smoke (within 1 wk)

"none" "passive" "smoker"

Pre-existing medical conditions

"none" "diabetes" "heart disease" "asthma"

"chronic lung disease" "chronic kidney disease"

"chronic liver disease" "chronic hematologic disease"

"neuromuscular dysfunction" "immune compromised"

Other: _____

Antimicrobial for this illness before admission

"Yes" "No" "Unsure"

"amox/penicillin ___d" "amox/clav ___d"

"1st ceph(cephalexin) ___d" "anti-TB therapy ___d"

"2nd ceph(cefuroxime) ___d" "cotrimoxazole ___d"

"doxy/tetracycline ___d" "metronidazole ___d"

"nitrofurantoin ___d" "erythro/clarithro ___d"

"FQ (e.g. cipro) ___d" "anti-viral ___d"

"other" _____d

Obtained from "GP" "OPD" "Pharmacist"

"Friend/ relative" "Other" _____

Flu vaccination "≤ 1 year" ">1 year" "never"

Impact of Current Illness

How much (___ rupees) did you/ your family

spend on medicine (pharmacy) for this illness?

How much on medical visit (private clinic,

government hospital, other.....)? ___ rupees

How much on travel (private clinic/government

hospital/pharmacy/ other...)? ___ rupees

How much work/school (___ day(s) ___ hrs) missed?

How much work (___ day(s) ___ hrs) did your

caretaker (specify: _____) miss for this

illness?

SYMPTOMS IN LAST 7 Days

Major(1^o) Symptom _____ Onset ___/___/___
DD MMM YR

REVIEW YES #DAYS NO UNSURE

Fever/ chills _____ " " " "

Sudden hearing loss _____ " " " "

Ear ache _____ " " " "

Runny nose/congestion _____ " " " "

Cough _____ " " " "

"dry" "productive" "bloody"

Sore throat _____ " " " "

Short of breath _____ " " " "

Pain with breathing _____ " " " "

Eating less _____ " " " "

Vomiting _____ " " " "

Diarrhea (> 3x/24h) _____ " " " "

Abdominal pain _____ " " " "

Painful urination _____ " " " "

Decreased urination _____ " " " "

Headache _____ " " " "

Fatigue/lethargy _____ " " " "

Convulsions _____ " " " "

Joint pain _____ " " " "

Muscle pain _____ " " " "

Rash _____ " " " "

Bleeding _____ " " " "

Pregnancy _____ wks " " " NA

EXAM FINDINGS on admission or enrollment

1. Temp: ___ . ___ °F Circle: oral, tym, axil, rectal

2. Resp rate ___ HR ___

3. Photophobia "Yes" "No" "Unsure"

4. Injected pharynx "Yes" "No" "Unsure"

5. Throat exudate "Yes" "No" "Unsure"

6. Normal breath sounds "Yes" "No"

7. Wheezing "Yes" "No"

Pulse oximetry

1. Heart Rate ___ /minute 2. SaO2 ___ %

OPD doctor's CLINICAL DIAGNOSIS

"Influenza" "RSV" "Strep pharyngitis"

"Tuberculosis" "Pneumonia" "Other viral fever"

"Upper resp. illness" "Lower resp. illness"

"Dengue" "Chikungunya" "Leptospirosis"

"Scrub Typhus" "Rickettsiae, other"

"Non-infectious" "Other" _____

Antibiotic prescribed "Yes" "No" "IM" "oral"

"amox/penicillin ___d" "amox/clav ___d"

"1st ceph(cephalexin) ___d" "anti-TB therapy ___d"

"2nd ceph(cefuroxime) ___d" "cotrimoxazole ___d"

"doxy/tetracycline ___d" "metronidazole ___d"

"nitrofurantoin ___d" "erythro/clarithro ___d"

"FQ (e.g. cipro) ___d" "anti-viral ___d"

"other" _____d

Diagnostic tests ordered "Yes" "No"

"Full blood count" "Creatinine" "Blood culture"

"CXR" "Urinalysis" "Urine culture"

Other _____

Admitted to the hospital? "Yes" "No"

Rapid flu result: ___A+ ___B+ ___Neg ___Invalid

___Nasal ___NP ___L ___R

PCR sample: ___Nasal ___NP ___L ___R

References

- Abeyssekera, R. A., Imbulpitiya, I. V. B., Ponnampereuma, S., & Kularatne, S. A. M. (2013). Influenza B infection, an underestimated killer– an experience at a Tertiary care Hospital– Sri Lanka. *Sri Lankan Journal of Infectious Diseases*, 3(1), 40–44.
- Attygalle, R. (2013, July 13). Getting vaccinated the proper way. *The Island*. Colombo.
- Azziz Baumgartner, E., Dao, C. N., Nasreen, S., Bhuiyan, M. U., Mah-E-Muneer, S., Al Mamun, A., ... Bresee, J. (2012). Seasonality, timing, and climate drivers of influenza activity worldwide. *The Journal of Infectious Diseases*, 206(6), 838–46. doi:10.1093/infdis/jis467
- Becton Dickinson. (2014). BD Veritor System - CLIA-waived for rapid detection of Flu A+B. Retrieved May 31, 2014, from <http://www.bd.com/ds/productCenter/256045.asp>
- Bhavnani, D., Phatinawin, L., Chantra, S., Olsen, S. J., & Simmerman, J. M. (2007). The Influence of Rapid Influenza Diagnostic Testing on Antibiotic Prescribing Patterns in Rural Thailand. *International Journal of Infectious Diseases*, 11(4), 355–9.
- Bonner, A. B., Monroe, K. W., Talley, L. I., Klasner, A. E., & Kimberlin, D. W. (2003). Impact of the Rapid Diagnosis of Influenza on Physician Decision-Making and Patient Management in the Pediatric Emergency Department: Results of a Randomized, Prospective, Controlled Trial. *Pediatrics*, 112, 363–367.
- Brown, D. W., Taylor, R., Rogers, A., Weiser, R., & Kelley, M. (2003). Antibiotic Prescriptions Associated with Outpatient Visits for Acute Upper Respiratory Tract Infections among Adult Medicaid Recipients in North Carolina. *NC Med J*, 64(4).
- Centers for Disease Control and Prevention. (2013a). Estimated influenza illnesses and hospitalizations averted by influenza vaccination-- United States, 2012- 13 influenza season. *MMWR*, 62(49), 993–6.
- Centers for Disease Control and Prevention. (2013b). Get smart: know when antibiotics work. Retrieved May 30, 2014, from <http://www.cdc.gov/getsmart/campaign-materials/about-campaign.html>
- Central Bank of Sri Lanka. (2014). Current Economic Indicators. Retrieved June 29, 2014, from http://www.cbsl.gov.lk/htm/english/_cei/er/e_1.asp

- Christiansen, K., Carbon, C., & Cars, O. (2002). Moving from recommendation to implementation and audit: Part 2. Review of interventions and audit. *Clinical microbiology and infection*, 8(Suppl 2), 107–28.
- Donnelly, J. P., Baddley, J. W., & Wang, H. E. (2014). Antibiotic utilization for acute respiratory tract infections in U.S. emergency departments. *Antimicrobial Agents and Chemotherapy*, 58(3), 1451–7.
- Duke University School of Medicine. (2011). Teaching Hospital at Karapitiya. Retrieved May 31, 2014, from <http://dukeglobalhealth.org/global-partners/sri-lanka>
- Epidemiology Unit, Ministry of Health. (2005). *Influenza pandemic preparedness and response*. *AJN, American Journal of Nursing* (Vol. 105, pp. 73–74). Colombo.
- Esposito, S., Marchisio, P., Morelli, P., Crovari, P., & Principi, N. (2003). Effect of a Rapid Influenza Diagnosis. *Archives of Disease in Childhood*, 88(6), 525–6.
- Falsey, A. R., Murata, Y., & Walsh, E. E. (2007). Impact of Rapid Diagnosis on Management of Adults Hospitalized With Influenza. *Archives of Internal Medicine*, 167, 354–360.
- Fowlkes, A., Giorgi, A., Erdman, D., Temte, J., Goodin, K., Di Lonardo, S., ... Finelli, L. (2014). Viruses Associated With Acute Respiratory Infections and Influenza-like Illness Among Outpatients From the Influenza Incidence Surveillance Project, 2010–2011. *The Journal of Infectious Diseases*, 209, 1715– 1725.
- Galle Municipal Council. (2010). Galle Municipal Council. Retrieved May 31, 2014, from <http://www.galle.mc.gov.lk/>
- Gill, J. M., Fleischut, P., Haas, S., Pellini, B., Crawford, A., & Nash, D. B. (2006). Use of antibiotics for adult upper respiratory infections in outpatient settings: a national ambulatory network study. *Family medicine*, 38(5), 349–54.
- Grijalva, C. G., Griffin, M. R., & Page, P. (2014). Antibiotic Prescription Rates for Acute Respiratory Tract Infections in US Ambulatory Settings. *JAMA*, 302(7), 758– 766.
- Holloway, K. A. (2011). Promoting the rational use of antibiotics. *Regional Health Forum*, 15(1), 122–130.

- Jefferson, T., Ma, J., Doshi, P., Cb, D. M., Hama, R., Mj, T., ... Cj, H. (2014). Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children (Review). *Cochrane Database Syst Rev*, Apr 10(4).
- Kono, J., Jonduo, M. H., Omena, M., Siba, P. M., & Horwood, P. F. (2014). Viruses Associated With Influenza-Like-Illnesses in Papua New Guinea, 2010. *Journal of Medical Virology*, 86, 899–904.
- Lam, T. P., & Lam, K. F. (2003). What are the non-biomedical reasons which make family doctors over-prescribe antibiotics for upper respiratory tract infection in a mixed private/ public Asian setting? *Journal of Clinical Pharmacy and Therapeutics*, 28(3), 197–201.
- Linder, J. a, Singer, D. E., & Stafford, R. S. (2003). Association between antibiotic prescribing and visit duration in adults with upper respiratory tract infections. *Clinical therapeutics*, 25(9), 2419–30.
- Lozano, R., Naghavi, M., Foreman, K., Lim, S., Shibuya, K., Aboyans, V., ... Ahn, S. Y. (2012). Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*, 380(9859), 2095–128.
- Lucas, M. N., Liyanage, U. A., & Lokukankanamage, L. K. U. I. (2001). A study of antibiotic usage in acute respiratory infections in children. *Sri Lankan Journal of Child Health*, 7, 5–7.
- Moore, M., Kelly, J., & Williamson, I. (2014). Delayed antibiotic prescribing strategies for respiratory tract infections in primary care: pragmatic, factorial, randomised controlled trial. *BMJ*, 1606(March), 1–8.
- Noyola, D. E., & Demmler, G. J. (2000). Effect of Rapid Diagnosis on Management of Influenza A infections, 19(4), 303–307.
- Peasah, S. K., Azziz-Baumgartner, E., Breese, J., Meltzer, M. I., & Widdowson, M.-A. (2013). Influenza cost and cost-effectiveness studies globally--a review. *Vaccine*, 31(46), 5339–48.
- Peltola, V., & Ruuskanen, O. (2008). Editorial commentary: Respiratory viral infections in developing countries: common, severe, and unrecognized. *Clinical Infectious Diseases*, 46(1), 58–60.

- Shiley, K., Nadolski, G., Mickus, T., Fishman, O., & Lautenbach, E. (2011). Differences in the epidemiological characteristics and clinical outcomes of pandemic (H1N1) 2009 influenza, compared with seasonal influenza. *Infect Control Hosp Epidemiol*, 31(7), 676–682.
- Sri Lanka Medical Association. (2012). *SLMA Guidelines on the Use of Antimicrobial Agents*. Colombo.
- Tamerius, J. D., Shaman, J., Alonso, W. J., Bloom-feshbach, K., Uejio, C. K., & Comrie, A. (2013). Environmental Predictors of Seasonal Influenza Epidemics across Temperate and Tropical Climates. *PLoS Pathogens*, 9(3).
- Tan, X. Q., Zhao, X., Lee, V. J., Loh, J. P., Tan, B. H., Koh, W. H., ... Cook, A. R. (2014). Respiratory viral pathogens among Singapore military servicemen 2009 – 2012: epidemiology and clinical characteristics. *BMC infectious diseases*, 14(1), 204.
- Willem, L., Van Kerckhove, K., Chao, D. L., Hens, N., & Beutels, P. (2012). A nice day for an infection? Weather conditions and social contact patterns relevant to influenza transmission. *PloS one*, 7(11), e48695.
- The World Bank. (2014). Sri Lanka. Retrieved June 28, 2014, from <http://data.worldbank.org/country/sri-lanka>
- World Health Organization. (2009). *Medicines use in primary care in developing and transitional countries*.
- World Health Organization. (2010). *Sex, gender and influenza*.
- World Health Organization. (2012). *WHO Interim Global Epidemiological Surveillance Standards for Influenza*.
- World Health Organization. (2013). *Sri Lanka- Country cooperation strategy at a glance*.
- World Health Organization. (2014). FluNet. Retrieved May 31, 2014, from http://www.who.int/influenza/gisrs_laboratory/flunet/en/