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Influenza is more common than Middle East respiratory syndrome coronavirus (MERS-CoV) among hospitalized adult Saudi patients

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Abstract:

Background: Since the initial description of Middle East Respiratory Syndrome Coronavirus (MERS-CoV), we adopted a systematic process of screening admitted patients with community acquired pneumonia. Here, we report the result of the surveillance activity in a general hospital in Saudi Arabia over a four year period.

Materials and Methods: All admitted patients with community acquired pneumonia from 2012 to 2016 were tested for MERS-CoV. In addition, testing for influenza viruses was carried out starting April 2015.

Results: During the study period, a total of 2657 patients were screened for MERS-CoV and only 20 (0.74%) tested positive. From January 2015 to December 2016, a total of 1644 patients were tested for both MERS-CoV and influenza. None of the patients tested positive for MERS-CoV and 271 (16.4%) were positive for influenza. The detected influenza viruses were Influenza A (107, 6.5%), pandemic 2009 H1N1 (n= 120, 7.3%), and Influenza B (n=44, 2.7%). Pandemic H1N1 was the most common influenza in 2015 with a peak in peaked October to December and influenza A other than H1N1 was more common in 2016 with a peak in August and then October to December.

Conclusions: MERS-CoV was a rare cause of community acquired pneumonia and other viral causes including influenza were much more common. Thus, admitted patients are potentially manageable with Oseltamivir or Zanamivir therapy.

Introduction:

The emergence of the Middle East respiratory syndrome coronavirus (MERS-CoV) in September 2012 had attracted international attention. The virus was initially isolated from a patient with a fatal community acquired pneumonia (CAP) in Saudi Arabia [1]. Since then, multiple hospital outbreaks occurred within Saudi Arabia [2–7] and outside Saudi Arabia [8–11]. As of May 1st, 2017, the World Health Organization reported 1952 laboratory-confirmed cases worldwide and at least 693 related deaths [12]. A wide-spectrum of MERS-CoV infection was described and ranges from mild to severe and fulminant infections leading to severe acute respiratory disease [2,13–15]. In the Kingdom of Saudi Arabia, the number of MERS-CoV cases was 1601 as of May 6th, 2017 [16]. Since most of the cases of MERS-CoV in Saudi Arabia occurred due to intra- and inter-hospital transmissions, there was an increased amplification of the transmission [2–4,9–11,17]. Early detection and isolation of patients with MERS-CoV infection remains an important factor for the control of MERS-CoV transmission [18,19]. One of the goals of the surveillance of emerging respiratory viruses is the rapid and early identification and placement of control measures [20]. Following the initial description of the disease [1], the ministry of health in the Kingdom of Saudi Arabia put in place a surveillance and screening program for admitted patients with respiratory illness [21]. Similarly, we adopted universal screening of admitted patients with community acquired pneumonia. Here, we report the result of the surveillance activity in a general hospital in Saudi Arabia over a four year period.

Materials and Methods:

The study was conducted at a 350-bed general hospital, which also accepts referred patients. The hospital provides medical care for about 160,000 individuals eligible for medical care. The hospital has 5 intensive care units (cardiac, medical, surgical, pediatric, and neonatal) [22]. All admitted patients with community acquired pneumonia from 2012 to 2016 were tested for MERS-CoV. The case definition of suspected MERS-CoV was an acute febrile respiratory illness (fever, cough, or dyspnea) with radiographic evidence of pneumonia [22]. We collected data for all suspected patients using a standard Microsoft Excel data collection sheet. Both electronic and paper medical records were reviewed. We recorded the age and the date of admission and the MERS-CoV and influenza results. The study was approved by the Johns Hopkins Aramco Healthcare Institutional Review Board (IRB).

MERS-CoV and Influenza Testing:

Suspected patients had either Dacron-flocked nasopharyngeal swabs, or sputum testing for MERS-CoV. The testing was done atthe Saudi Ministry of Health MERS-CoV laboratory and at the main hospital. Clinical samples were screened with real-time reverse-transcriptase (RT)-PCR as described previously [23]. The test amplified both the upstream E protein (upE gene) and ORF1a for MERS-CoV and if both assays were positive then the diagnosis of MERS-CoV was made, as described previously [14]. The influenza test was carried out at the Johns Hopkins Aramco Healthcare Centre, Dhahran, using the Cepheid® Xpert Flu assay multiplex real-time PCR. The tested influenza viruses were pandemic 2009 H1N1, Influenza A (other than H1N1), and Influenza B. The test was systematically carried out starting April 2015.

85

86

87 **Statistical Analysis:**

88 Statistical analysis was done using Excel and descriptive analyses were done for demographic,
89 results of the tests and the monthly number of cases. Minitab® (Minitab Inc. Version 17,
90 PA16801, USA; 2017) was used to calculate the mean age (± SD) of patients with influenza.

91 **Results:**

92 During the study period from 2013 to 2016, a total of 2657 patients were screened for MERS-
93 CoV and only 20 (0.74%) tested positive. During the first two years (April 2013-March 2015), a
94 total of 1013 patients were screened for MERS-CoV. Only 1.8% of them were positive for
95 MERS-CoV (Table 1) and unfortunately these were not systematically screened for influenza.
96 There was an increased number of tests in November 2015-March 2016 (Figure 1).

97 From April 2015 to December 2016, a total of 1644 patients were tested for both MERS-CoV
98 and influenza. None of the patients tested positive for MERS-CoV and 271 (16.4%) were
99 positive for influenza. The detected influenza viruses were Influenza A (107, 6.5%), pandemic
100 2009 H1N1 (n= 120, 7.3%), and Influenza B (n=44, 2.7%) (Table 1 and figure 2). It is
101 interesting to note the pattern of the influenza in 2015 and 2016 (figure 3). Pandemic H1N1 was
102 the most common influenza in 2015 and influenza A other than H1N1 was more common in
103 2016. The 2015 influenza season peaked October to December and the 2016 season had a peak
104 in August and then October to December (figure 3). There was a significant difference in the
105 mean age (± SD; 95% CI) of patients with H1N1 and other influenza (Figure 4). The mean age

106 (± SD; 95% CI) was 45.09 (±24.32; 40.85, 49.33) for H1N1, 63.70 (±20.34; 59.21, 68.19) for
107 influenza A, 55.11 (±25.27; 48.11, 62.12) for Influenza B, and 61.28 (±23.82; 60.03, 62.54) for
108 influenza negative patients ($P < 0.0001$).

109 **Discussion:**

110 In this study, we presented the surveillance data on MERS-CoV over a four year period and the
111 surveillance for influenza over a two year period. MERS-CoV was only detected in 20 (0.75%)
112 from a total of 2657 patients as detailed in previous publication [22,24]. The earliest
113 surveillance study from Saudi Arabia was done from 1 October 2012 to 30 September 2013 and
114 tested a total of 5065 samples [21]. In that study, the MERS positivity rate was 2% [21]. A
115 second surveillance of MERS-CoV in Saudi Arabia was conducted from April 1, 2015 to
116 February 1, 2016 and included a total of 57,363 suspected MERS cases [25]. The study showed
117 only 384 (0.7%) MERS-CoV positive cases [25]. In a study in the United States, two (0.4%)
118 imported cases were detected among 490 patients-under investigation in 2013-2014 [26]. In a
119 surveillance study of 1586 unique persons from the United Arab Emirates between January 1,
120 2013and April 17, 2014, 41 (3%) tested positive for MERS-CoV infection [27]. In the South
121 Korea outbreak, 184 (1%) had MERS among 16752 suspected cases [28]. In a small study from
122 Saudi Arabia, MERS-CoV was not detected in 182 cases tested November 2013 and January
123 2014 (winter time) [29]. Thus, the overall positivity of MERS-CoV among a large cohort
124 remains low. There is a need for a better tool to identify patients with high probability of
125 MERS-CoV. However, a case control study and a large cohort study did not reveal significant
126 predictor of MERS-CoV infection [22,30].

The monthly frequency of suspected MERS cases that were tested showed variation with an apparent increase in the tested number during November 2015-March 2016. This apparent increase likely represented an increased activity of influenza during that time. There was no relation to the Hajj season as it occurred during September 21-26, 2015 (Figure 1). In addition at that time, there were no known outbreaks in the Kingdom of Saudi Arabia to account for such an increase in the testing. The 2015 outbreaks occurred in Al-Hasa in May 2015 [31] and in Riyadh in August 2015 [7,32,33]. Previous studies had shown increased testing of patients for MERS-CoV during outbreaks [4]. The In the current study, 2015 season was predominated by 2009 pandemic H1N1 whereas influenza A was more common during 2016. Similarly, in the United States the 2014-2015 season was predominated by pandemic H1N1 and H3N2 was more common during the 2016-2017 season [34,35].We found that influenza rather than MERS-CoV was more common among the tested patients. The findings are also consistent with other studies among travelers and pilgrims where influenza far exceeded MERS [36–40]. Similarly, in a small study in Saudi Arabia, influenza viruses were detected in 16% [29]. Similarly, among a small study of 52 suspected MERS cases in the United States of America, Influenza was the most commonly (35%) identified respiratory agent [41] and another study found influenza A and B in 11% of 296 investigated patients [26]. Thus, it is important to test for common respiratory pathogens such as influenza viruses and it should be noted that identification of a respiratory pathogen should not exclude MERS-CoV testing [42]. One report indicated co-infection with influenza and MERS in four patients [43]. However, epidemiologic differences between different countries should remain as an important predictor of the existence of MERS-CoV infection.

The mean age of patients with H1N1 was younger than the other influenza patients of at least 10 years (45.09 vs. 63.70 for influenza A, 55.11 for Influenza B, and 61.28 for influenza negative

patients (P < 0.0001). The inital cases of pandemic 2009 H1N1 were also younger than the influenza negative patients [44]. In a small study of 196 patients, influenza B patients were younger than other influenza [45] and in another study the mean age was lower for patients with influenza B (16.4 yr) than (H1N1) pdm09 influenza infection. However, these studies included children and thus are not compareable with the present study [46].

Similar results were obtained in travelers returning from the Middle East. These studies showed the lack of MERS-CoV among travelers and that influenza was more common among French travelers [47,48], Austrian returning pilgrims [40], British travelers [49], German travelers [50], and travelers to California, United States [41]. The presence of influenza infection among those travelrs stress the need for influenza vaccination in travelers, notably tfor those going for the Hajj and Umrah in Saudi Arabia.

In conclusion, MERS-CoV was a rare cause of CAP and other viral causes including influenza are much more common. The epidemiology of influenza mirrored the epidemiology of influenza worldwide. The study highlights the importance of the surveillance system to elucidate the epidemiology of respiratory infections in order to formulate appropriate control measures. Inter-hospital and intra-hospital transmission of MERS-CoV infection is an important element of the transmission of this virus and it is imperative to continue to have early recognition of cases and constant application of infection control measures to abort the hospital transmissions of the virus [18,19].

Conflict of interest: all authors have no conflict of interest to declare

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Tables and Figures Legend:

Table 1: Number of positive tests for influenza and MERS-CoV

Figure 1: Monthly number of patients who were tested for MERS-CoV

Figure 2: Monthly Influenza Type from April 2015 to December 2016

Figure 3: A Line graph showing the monthly number of isolated influenza by type

Figure 4: Interval Plot of Age and 95% Confidence Interval of Age among Influenza Patients

Table 1: Number of positive tests for influenza and MERS-CoV in relation to the study period

Study Period	MERS-CoV	Influenza A	H1N1	Influenza B	Grand Total
4/2013-3/2015	20 (1.8)	ND	ND	ND	1092
4/2015-12/2016	0 (0)	107 (6.5)	120 (7.2)	44 (2.6)	1644
Overall	20 (0.74)				2736

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Figure 1: Monthly number of patients who were tested for MERS-CoV and the time of occurrence of major outbreaks

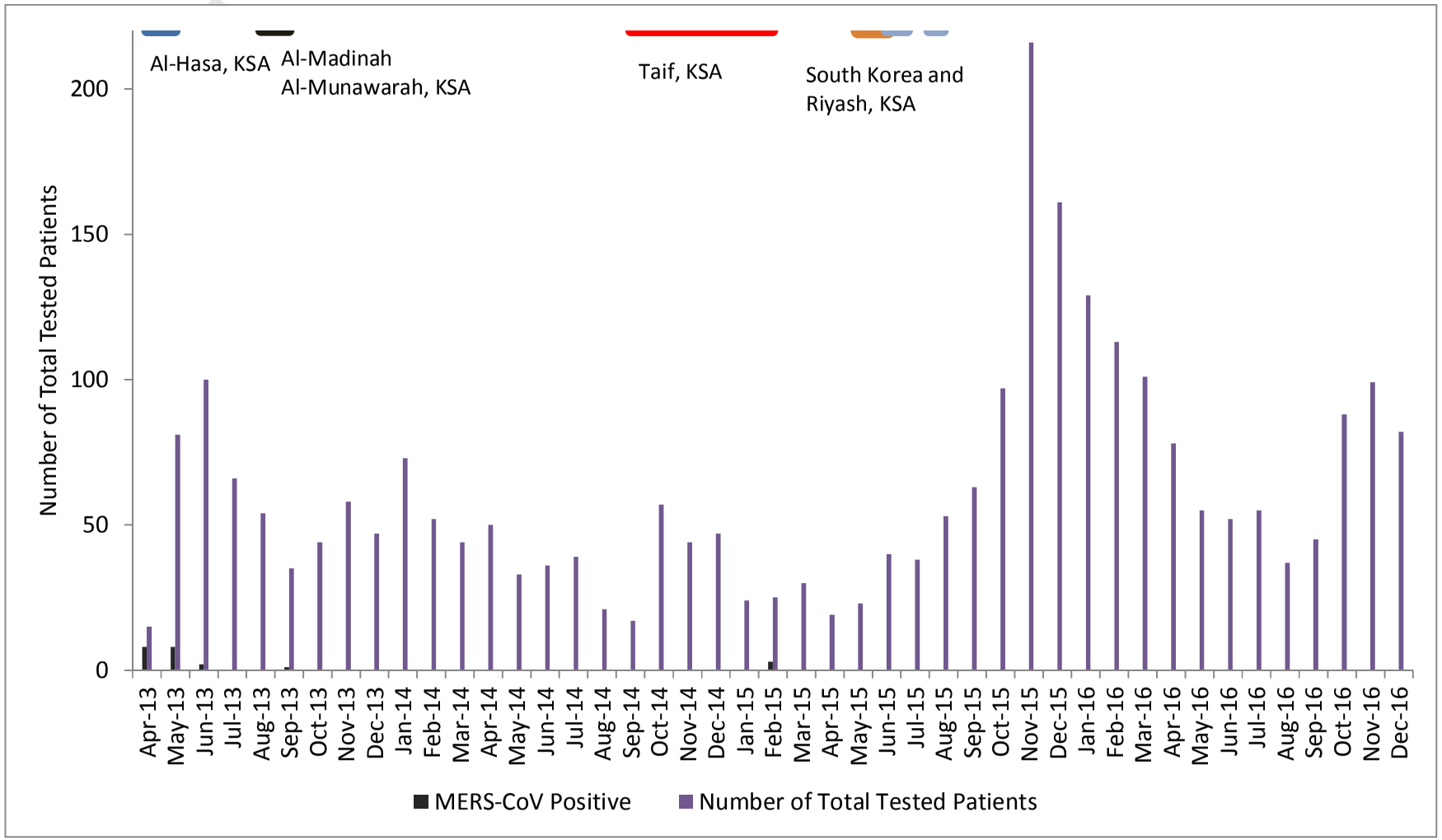


Figure 2: Monthly Influenza Type from April 2015 to December 2016

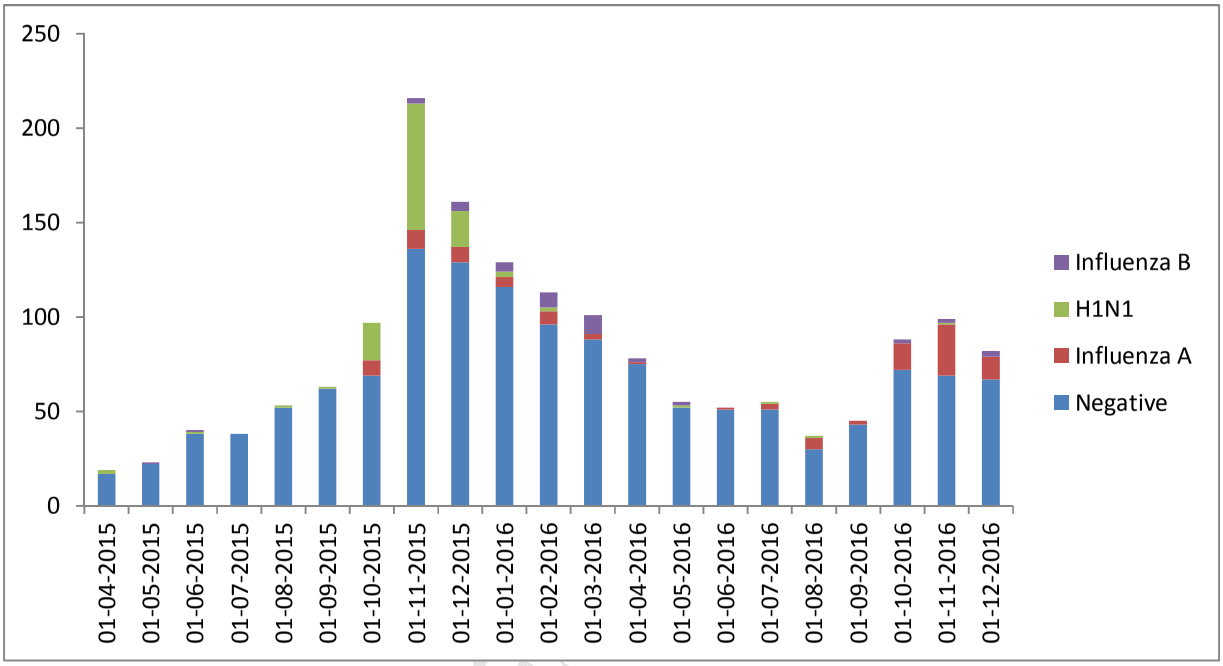
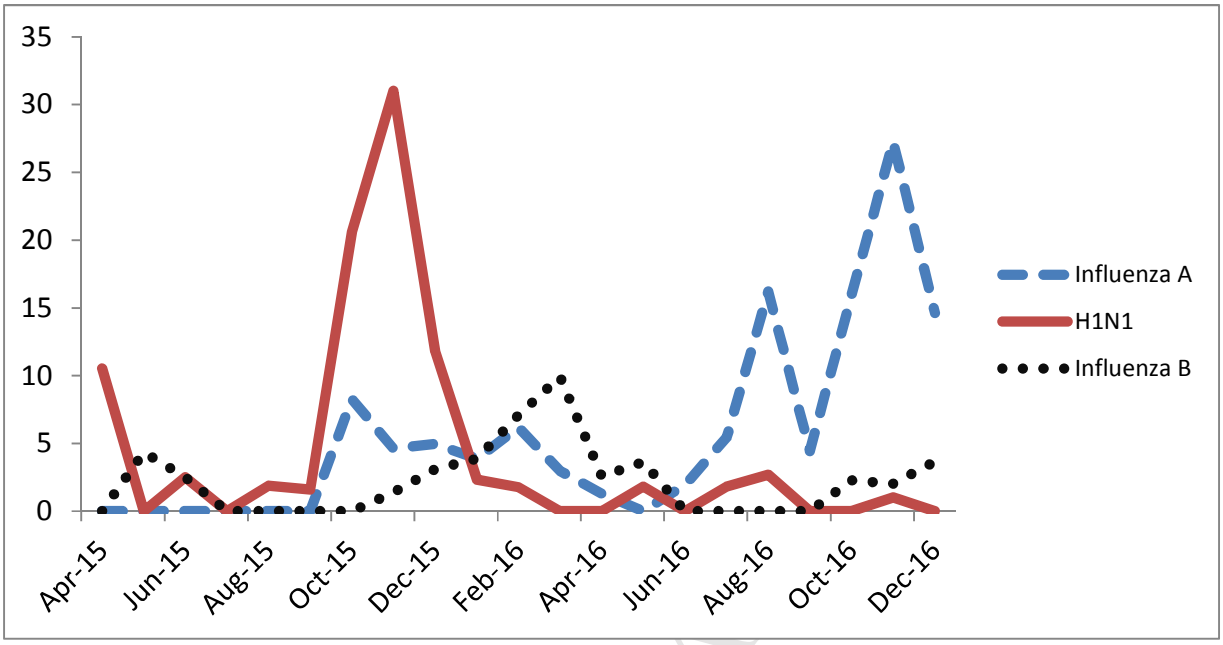


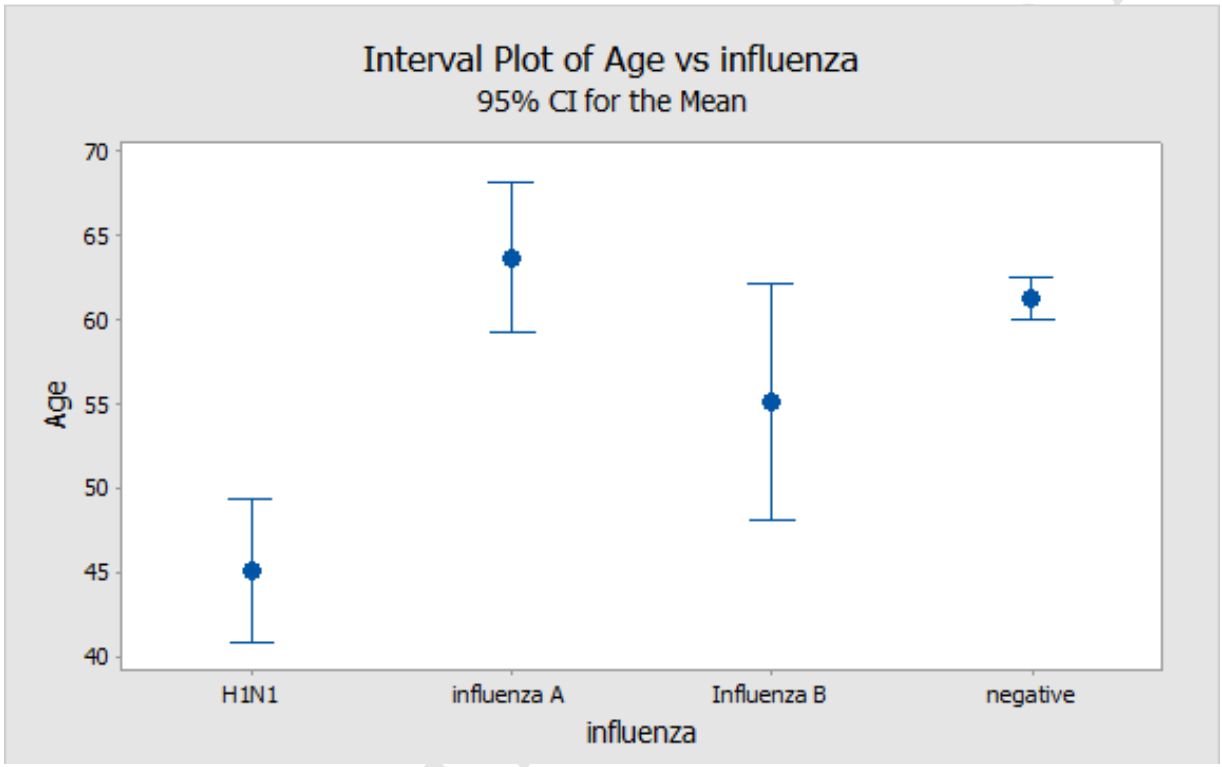
Figure 3: A Line graph showing the monthly number of isolated influenza by type



402 **Figure 4: Interval Plot of Age and 95% Confidence Interval of Age among Influenza**

403 **Patients**

404



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