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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

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Supplement

Supplementary methods

Characteristics of study sites

The rural site in Mpumalanga Province is part of a health and socio-demographic surveillance site (HDSS) at the Medical Research Council (MRC)/University of Witwatersrand Rural Public Health and Health Transitions Research Unit, Agincourt. There a population of approximately 116,000 people in 31 villages in the Bushbuckridge District are under demographic surveillance.[1] The Bushbuckridge Municipality had an estimated population of 548,760 (53.54 per km²) in 2016 with a mean household size of 4.0 persons.[2] Grants and subsidies comprised 79.8% of 2015 household income. The majority of the population are Xitsonga-speaking members of the Shangaan ethnic group and approximately 30% are Mozambican refugees of the same ethnic group who settled in the area in the 1980s .[1,3] A 2012 survey estimated HIV prevalence of 14.1% in Mpumalanga Province.[4]

The urban site, Jouberton township in Klerksdorp, is located in the local municipality of Matlosana (population 417,282 in 2016) in North West Province with a mean household size of 3.1 persons.[2] Grants and subsidies comprised 22.8% of 2015 household income. Mining (gold, uranium) remains a primary driver of the local economy, but with significant declines in mining employment since the 1990s unemployment and poverty have significantly increased. Jouberton was estimated to have a population of 111,938 (4859 per km²) in the 2011 census and the predominant language is Tswana. A 2012 survey estimated HIV prevalence of 13.3% in North West Province.[4]

Household selection and participant enrolment

We selected households using different methods in each site. In Agincourt, each year we selected two villages out of 29 within the HDSS according to convenience considering proximity and burden of other studies within the site. Within these villages, households with >2 members were randomly selected. In Jouberton Township, a list of 450 random global positioning system (GPS) coordinates

were generated in the study area using Google Earth as previously described.[5] Study staff navigated to the coordinates and selected the nearest house within 30 meters of the location. If there was no dwelling within 30m the coordinates were discarded.

Participant enrolment was conducted during November and December of the year preceding the period of active follow up i.e. during 2016 for the 2017 cohort and during 2017 for the 2018 cohort. Study staff confirmed that the household contained >2 members and requested permission from the head of household to inform members about the study. After a minimum of three attempts, if the head of household was unavailable or a minor, the house was excluded. Study staff requested informed consent to participate in the study from all household members aged ≥18 years, assent from children aged 7 to 17 years, and consent from a parent or guardian for children younger than 18 years. Households where ≥80% of members consented were enrolled. Individuals who participated in the study were more likely to be female and less likely to be aged 15-44 years compared to individuals who did not participate within included households.[6]
At the rural site, characteristics of included households were similar to those of households within the HDSS that were not included.[6] However, when compared to individuals from the HDSS who were not included, included individuals were less likely to be aged 15-44 years, male, employed, or have completed secondary education, likely reflecting migrant worker patterns and the fact that within included households, males and individuals aged 15-44 years were less likely to participate in the study. At the urban site, characteristics of households and individuals included in PHIRST were similar to those of residents of Jouberton Township except that included households were more likely to be formal houses rather than shacks within informal settlements.

Data collection

Participants were followed up with twice-weekly visits from January through October of the year of active follow up, following enrolment during November-December of the previous year. Twice-

weekly follow up was from January through October to ensure that we captured the start of each year's influenza season at each site and to allow us to evaluate the presence of influenza transmission in communities outside of the winter influenza season which usually occurs from May through September. Intensive follow-up was stopped during November through December to allow for enrolment of the next years cohort.

Twice-weekly follow-up visits occurred on Monday-Wednesday and Thursday-Saturday. If a household withdrew from the study during January-April it was replaced by a new household for the remaining follow-up period. Symptom data for children was consistently collected from the individual identified as primary caregiver at the time of enrolment. A review of symptom data collected during 2016, revealed under-reporting, likely due to research fatigue among participants as well as the high complexity of the questionnaire, hence these data were not included. In 2017 and 2018, a number of measures were implemented to address research fatigue and improve the validity of symptom data. The symptom form was simplified to require the same data fields irrespective of symptom reporting, refresher training for field workers on symptom data collected was conducted every 1-2 months, participants were reminded at least monthly of the importance of consistently and validly reporting symptoms despite fatigue, field staff were encouraged to observe participants for the presence of visible clinical signs such as cough or runny nose and probe participants if not reported and regular supervisory visits were conducted with particular focus on quality of symptom data collection and cross checking observed clinical signs and symptoms with reported data.
Field workers received refresher training of different aspects of study implementation including data collection, specimen collection and use of online databases at least monthly. Site supervisors conducted regular (at least monthly) supervisory visits to assess study implementation in the field and external (teams from outside the study sites) supervisory visits were conducted quarterly.

Current tuberculosis was defined as an individual currently receiving treatment for tuberculosis. Previous tuberculosis was defined as a self-reported history of having been diagnosed with or treated for tuberculosis. All individuals reporting cough, weight loss or night sweats for >2 weeks were offered tuberculosis testing and any individuals testing positive during the study were classified as having current tuberculosis.

Written vaccination history was obtained for all children aged <5 years from patient-held immunisation records and, if needed, vaccination records at health facilities. Primary caregivers giving a history of the child never being vaccinated were recorded as unvaccinated.

Household income was evaluated through self-reporting by the head of household. For households where income varied from month to month, the head of household was asked to provide the average monthly household income over the previous 12 months.

Indoor respirable particulate matter (PM_4) mass concentrations were measured gravimetrically using filter-based sampling. Mixed cellulose ester filters were exposed daily for 24 hours in each household, for a period of one week, during both summer and winter. Indoor temperature was continuously monitored using Thermochorn iButton DS1922L sensors.

Quantitative urine cotinine tests were performed using the IMMULITE® 1000 Nicotine Metabolite Assay Kit (Siemens Medical Solutions Diagnostics, Gly Rhonwy, UK). HIV testing was offered to all participants on enrolment.

In 2018, four surveys of household contact using proximity monitors (www.sociopatterns.org) were conducted to capture information on intra-household contact patterns for three seasons (summer, autumn, and winter). To measure contacts of participants of the study outside the home,

participants were interviewed by field workers to complete a contact diary and time-use questionnaire for one day between August and October 2018.

Infants were defined as HIV exposed but uninfected if they were HIV-uninfected but the mother was HIV-infected. For HIV-infected individuals, specimens were collected for CD4+ T cell and HIV quantitative viral load testing at diagnosis or enrolment.

Laboratory methods

The FTD Flu/RSV detection assay (Fast Track Diagnostics, Luxembourg) has a reported sensitivity of 100% and a specificity of 100% according to a clinical validation study of 60 samples reported by the manufacturer.[7] All positive samples were sent for subtype or lineage determination and subtype or lineage was determined for 79% (723/917) of positive samples. All samples for which subtype or lineage could not be determined, were retested twice from a separate extract. Samples which were positive for ≥2 of 3 tests (61 influenza A and 133 influenza B) were included as positive. In years where only one influenza A subtype or B lineage was detected at a site, we assumed that influenza A or B positive samples that could not be subtyped or lineage typed were the dominant subtype/lineage for that year.

Definitions and statistical analyses

For rRTPCR positivity where subtype or lineage was not determined we assigned a subtype or lineage if the individual had a confirmed subtype or lineage of the same influenza type (A or B) within the two preceding or following visits (Supplementary figure 2). If a subtype could not be assigned using the described criterion, we considered an episode of infection of influenza A or B virus unsubtyped. We considered a new infection of the same subtype or lineage when the individual tested positive for the same subtype >2 weeks from the last day of previous positivity; else

we considered it the same episode. Episode duration was estimated from the first to the last day of influenza rRTPCR positivity with the same type/subtype/lineage.

For the main analysis of serial interval and HCIR, we included all secondary cases with PCR positivity <12 days after the index case. This cutoff period was chosen based on an examination of the distribution of serial intervals observed in our cohort (Figure 3). We observed a marked reduction in cases in household contacts after 12 days. Because this cutoff was somewhat arbitrary, we also performed sensitivity analyses estimating the HCIR with a longer (including all secondary cases irrespective of serial interval) and shorter (including all secondary cases with PCR positivity <7 days after the index cases) cutoff and explored factors associated with serial interval among the subset with serial interval <8 days.

For the analysis of factors associated with incidence we assessed overdispersion starting with a negative binomial model and retained a simpler Poisson model as there was no statistically significant overdispersion detected. Visits where there was no swab collected were treated as missing information. We used Taylor linearization as implemented by the "svy" command in Stata and described in Kish et al.[8] We set the study site as strata and the household as the primary sampling unit. or analyses by age group for each analysis we chose as reference the age group with the lowest point estimates and sufficient numbers so that we could present positive odds ratios for the other relevant groups. For models including age group of both the index case and household contact we used the same reference group for both.

Sensitivity analyses

For estimation of household cumulative infection risk (HCIR), a sensitivity analysis was conducted where individuals previously infected by the same subtype/lineage within the season were removed from the denominator. We performed sensitivity analyses of serial interval and HCIR including

156 individuals with serial interval <8 days or including all possible secondary cases irrespective of serial
157 interval (for HCIR only).
158
159 Ethics
160 The U.S. Centers for Disease Control and Prevention's Institutional Review Board relied on the local
161 review (#6840).

Supplementary results

Out of 90,041 potential follow up visits, we did not collect and test a swab for influenza for 8611 visits. Reasons for this were participant travelling (n=4177), missed visit (n=4070), reason not specified (n=364).

Among influenza-infected individuals with ≥1 symptom and who were attending school or work, symptoms associated with increased absenteeism were cough (79/125, 63% absenteeism with cough vs 16/43, 37% absenteeism without cough, p=0.003), headache (36/53, 68% absenteeism with headache vs 59/115 51% absenteeism without headache, p=0.043) and vomiting (6/6, 100% absenteeism with vomiting vs 89/162, 55% absenteeism without vomiting, p=0.029).

On univariate analysis of specific index case symptoms associated with increased influenza transmission, fever (HCIR 32/203, 16% in those with fever vs 77/885, 9% in those without fever, p=.003), cough (HCIR 63/439, 14% in those with cough vs 46/649, 7% in those without cough, p<0.001), diarrhoea (HCIR 5/14, 36% in those with diarrhoea vs 104/1074, 10% in those without diarrhoea, p=0.001), runny nose (HCIR 65/394, 17% in those with runny nose vs 44/694, 6% in those without runny nose, p<0.001) chest pain (HCIR 9/41, 22% in those with chest pain vs 100/1047, 10% in those without chest pain, p=0.009), vomiting (HCIR 11/23, 48% in those with vomiting vs 98/1065, 9% in those without vomiting, p<0.001) and headache (HCIR 37/181, 20% in those with headache vs 72/907, 8% in those without headache, p<0.001) were all associated with increased transmission. On multivariable analysis in separate models each adjusting for index case and household member age group and duration of shedding and the individual symptom of interest, only runny nose (aOR 2.3, 95%CI 1.3-4.4), diarrhoea (aOR 9.2, 95% CI 1.3-67.1), chest pain (aOR 6.6, 95% CI 1.7-26.0), vomiting (aOR 10.5, 95% CI 2.7-40.4) and headache (aOR 2.9, 95% CI 1.5-5.7) remained associated with increased transmission.

While index cases aged 1-4 years were more likely to transmit influenza, only a small proportion of secondary cases from index cases aged <5 years were also aged <5 years (32/278, 12% of secondary cases <5 years, 122/278, 44% 5-18 years, 124/278, 45% ≥19 years). A slightly higher percentage of secondary cases from index cases aged ≥5 years were aged <5 years (149/861, 17% of secondary cases <5 years, 330/861, 38% 5-18 years, 382/861, 44% ≥19 years) (p=0.048).

Rates and proportion of infection, symptomatic illness and medically-attended illness varied by influenza A subtype and influenza B lineage (Figure 2, panel C). Age-specific incidence varied by influenza subtype and lineage, with the highest incidence per 100 person seasons for influenza A(H3N2) among individuals aged 13-18 years (21.1, 95% CI 15.0-29.6), for influenza A(H1N1)pdm09 among 1-4 years (20.6, 95% CI 14.6-29.1), for influenza B Victoria among <1 year (37.9, 95% CI 19.0-75.8) and for influenza B Yamagata among 13-18 years (11.5, 95% CI 7.2-18.2) (Supplementary table 8, Supplementary figure 6).

Supplementary discussion

Subtype-specific differences in influenza burden, age distribution and symptom profiles have been proposed since the early studies of household influenza burden and transmission in the 1960s,[9–11] with varying subtypes suggested to have higher incidence or symptomatic fractions. Interestingly, the overall rate of infection with influenza A (23.5/100 person seasons) and influenza B (20.2 per 100 person seasons) were similar despite annual variation in circulating types and subtypes. We did however observe notable differences in age-specific incidence by virus subtype although numbers were relatively small. Limited numbers in our study and historical studies as well as viral evolution and changing population immunity profiles limit our ability to make strong assertions about generalisable differences in subtype-specific epidemiology.

RESEARCH IN CONTEXT PANEL – FULL VERSION

Research in context

Evidence before this study

Burden

Seasonal influenza causes approximately 300,000-600,000 respiratory deaths globally annually, with the highest rates in sub-Saharan Africa.[1] The global SARS-CoV-2 pandemic has highlighted the importance of respiratory viruses with pandemic potential, including influenza, as a global public health threat. Understanding the community burden and transmission of seasonal influenza is paramount to guide the use of vaccination and non-pharmaceutical interventions and may inform pandemic preparedness.

A systematic review of the community infection prevalence of influenza was conducted in 2014.[2] Subsequent community-level cohort studies of influenza with polymerase chain reaction (PCR) and/or serologic confirmation were identified from the UK,[2] and New Zealand.[3] We did not identify

any studies of influenza community burden from Africa. These studies, including data from the USA,[4,5] UK,[2] Vietnam[6] and New Zealand,[3] identified annual community influenza infection rates ranging from 15%-35%.

Estimates of the proportion of influenza virus infections which are symptomatic range from 4%-28% and 65%-85% from outbreak investigations and serologic studies respectively.[7,8] Heterogeneity in estimates of asymptomatic fraction could be as a result of biological factors such as differences in illness severity following varied exposure intensity or because of differences in illness reporting or criteria for seroconversion. Few published studies on the symptomatic proportion by age exist, although the variation is plausible given changes in both illness severity and immunity with age.[8] A review found that 36%-71% of symptomatic influenza episodes have reported fever and 15%-40% of PCR-confirmed influenza cases seek medical care, with higher care-seeking among children.[2] Studies of the proportion of individuals infected with influenza each season have historically utilised paired blood samples taken from individuals before and after the influenza season, with infection defined by a four-fold rise in antibody titres. This approach may capture asymptomatic infections, but not the proportion of influenza infections associated with illness or the role of asymptomatic influenza infections in transmission, as the time of infection and transmission events are unknown.

Transmission

A systematic review of seasonal influenza household transmission studies identified several studies including one from Africa.[9] Additional transmission studies identified were a case ascertained study of influenza household transmission from Nicaragua, a clinical trial of oseltamivir efficacy against influenza transmission from Japan and a clinical trial of handwashing from Bangladesh. The secondary infection risk for PCR-confirmed influenza among household contacts ranged from 1%-38%. Whether asymptomatic individuals can transmit influenza remains an outstanding question.

Study designs used to assess influenza household transmission include case ascertained studies where index cases with influenza infection are identified, often through surveillance with household contacts followed up to identify subsequent influenza infections. Limitations of this approach include the possibility that the index case may not in fact be the first infection introduced into the household. In addition, symptomatic individuals identified through surveillance may have more severe illness than the general population potentially biasing estimates of transmission upward. Cohort studies aim to address these limitations by enrolling households at the beginning of the influenza season and following up all household members to identify infection and illness. Because of the extensive resources required, most cohort studies ascertain influenza infections using paired sera and restrict PCR testing to symptomatic individuals, limiting the ability to assess the role of asymptomatic individuals in transmission.

Added value of this study

We conducted a community burden and transmission study in a rural and an urban area of South Africa from 2017-2018, with systematic twice-weekly nasopharyngeal sampling of all household members irrespective of symptoms, collected at each visit, for 10 months of each year and sample testing for the presence of influenza by PCR. This allowed us to estimate the infection rate and the symptomatic fraction of influenza virus as well as the role of symptomatic and asymptomatic individuals in influenza virus transmission within different age groups. We collected and tested 81,430 nasopharyngeal swabs, of which 917 (1.1%) tested positive for influenza on PCR. Overall, 79% of households had at least one individual testing influenza positive each season, with an average of 1.7 new introductions and 2.3 infected individuals per infected household annually. On average, 37% of people were infected at least once with PCR-confirmed influenza each year. Incidence was similar in the urban and rural site. Repeat influenza infections within the same season were identified in 17% of individuals experiencing at least one influenza infection and were more common in children. The resulting incidence of PCR-confirmed influenza infection and illness was 43.6 and 24.4 per 100

person seasons respectively and was highest among children aged <5 years (67.4 and 49.9 per 100 person seasons respectively) and decreased with increasing age. Overall, 56% of infections were associated with ≥1 symptom and 35% of these had fever and cough (World Health Organization influenza-like illness case definition recommended for influenza surveillance (ILI)). The proportion of symptomatic infections was higher in children aged <5 years (74% in this age group vs 39% in those aged 19-44 years). Among individuals with influenza-like illness, 29% sought medical care. The rate of medically-attended influenza-associated illness was 6.0 per 100 person seasons and was highest in the extremes of age. Overall, there was influenza transmission to 10% of household contacts of an index case. Transmission was highest among children and individuals with ≥2 symptoms (17%); however, asymptomatic individuals did transmit influenza to 6% of household contacts. HIV-infection, affecting 16% (167/1075) of individuals, was not associated with increased incidence or HCIR.

Implications of all the available evidence

The burden of PCR-confirmed influenza infection is high in a rural and an urban African setting, with over three-quarters of households and over one in three individuals experiencing at least one influenza infection each year. Repeat infections are common, affecting >15% of infected individuals. Just over half of all infections are symptomatic and one fifth experience ILI. Medically-attended ILI, as captured through WHO-recommended influenza surveillance programmes makes up only 10% of all illness and 41% of medically-attended illness, suggesting substantial underestimation of disease burden through these programmes. Young children experience the highest burden of influenza infections and are more likely to transmit influenza to their household contacts. The high burden of asymptomatic influenza infections in the community, together with the fact that asymptomatic individuals transmit influenza to approximately 6% of household contacts suggests that asymptomatic individuals may be an important driver of influenza transmission. Our study has implications for the utilisation of non-pharmaceutical interventions and vaccination strategies

targeting children to prevent influenza transmission. A similar study is being implemented to assess burden and transmission of SARS-CoV-2.

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Supplementary table 1: Proportion of households testing influenza positive, number of clusters and mean cluster size, attack rate and rates of influenza infections per 100 person season by year and site, at a rural and an urban site, South Africa, 2017-2018

Year	Site	Household level			Individual level				
		Proportion of households with at least one person testing influenza positive n/N (%)	Clusters per infected household Mean (Range) [a]	Infected individuals per household with at least one infected individual Mean (Range)[b]	Person seasons of follow up	At least one infection episode [c]	Rate per 100 person seasons (at least one episode) (95% CI) [c]	Total infection episodes [d]	Rate per 100 person seasons (multiple episodes) (95% CI) [d]
2017-2018	Rural and urban	178/225 (79)	1.7 (1-4)	2.3 (1-10)	1097.0	408	37.2 (33.8-41.0)	478	43.6 (39.8-47.7)
2017-2018	Rural	89/109 (82)	1.7 (1-4)	2.3 (1-10)	555.3	204	36.7 (32.0-42.1)	243	43.8 (38.6-49.6)
2017-2018	Urban	89/116 (77)	1.6 (1-4)	2.3 (1-6)	541.8	204	37.7 (32.8-43.2)	235	43.4 (38.2-49.3)
2017	Rural and urban	90/108 (83)	1.7 (1-4)	2.3 (1-10)	552.6	208	37.6 (32.9-43.1)	240	43.4 (38.3-49.3)
2017	Rural	3/53 (81)	1.6 (1-4)	2.3 (1-10)	283.2	97	34.3 (28.1-41.8)	113	39.9 (33.2-48.0)
2017	Urban	47/55 (85)	1.8 (1-4)	2.4 (1-6)	269.4	111	41.2 (34.2-49.6)	127	47.1 (39.6-56.1)
2018	Rural and urban	88/117 (75)	1.6 (1-3)	2.3 (1-5)	544.5	200	36.7 (32.0-42.2)	238	43.7 (38.5-49.6)
2018	Rural	46/56 (82)	1.8 (1-3)	2.3 (1-5)	272.1	107	39.3 (32.5-47.5)	130	47.8 (40.2-56.7)
2018	Urban	42/61 (69)	1.4 (1-3)	2.2 (1-5)	272.4	93	34.1 (27.9-41.8)	108	39.7 (32.8-47.9)

[a]Among 178 households experiencing at least 1 cluster of influenza infection, 87 (49%) had 1 cluster, 63 (35%) had 2 clusters, 25 (14%) had 3 clusters and 3 (2%) had 4 clusters [b]Among 298 clusters of influenza infection, 185 (62%) involved only 1 infected individual within the household [c]Individuals testing influenza positive at least once during follow up counted once, incidence estimated as number of episodes divided by the person time under observation [d]Includes repeat episodes, among 408 individuals who experienced at least one influenza episode in a season, 339 (83%) had 1 episode, 66 (16%) had 2 episodes and 3 (1%) had 3 episodes, incidence estimated as number of episodes divided by the person time under observation. Among the 480 episodes, includes 2 episodes of mixed infection (both influenza A(H3N2)/B Yamagata in 2017).

370 CI – confidence interval, N-number

Supplementary table 2: Rates of influenza infections and influenza-associated illness per 100 person seasons by age group, at a rural and an urban site, South Africa, 2017-2018

Age group (years)	Infections Person seasons of follow up	At least one episode [a]	Rate (at least one episode) (95% CI) [a]	Total episodes [b]	Rate (multiple episodes) (95% CI) [b]	Repeat infections n/N (%)
<1	21.1	10	47.4 (25.5-88.0)	14	66.3 (39.3-112.0)	4/14 (29)
1-4	155.3	87	56.0 (45.4-69.1)	105	67.6 (55.8-81.8)	18/105 (17)
5-12	302.0	129	42.7 (35.9-50.8)	154	51.0 (43.5-59.7)	25/154 (16)
13-18	156.6	59	37.7 (29.2-48.6)	70	44.7 (35.4-56.5)	11/70 (16)
19-44	282.9	76	26.9 (21.5-33.6)	84	29.7 (24.0-36.8)	8/84 (10)
45-64	134.9	37	27.4 (19.9-37.9)	40	29.7 (21.8-40.4)	3/40 (8)
≥65	44.2	10	22.6 (12.2-42.0)	11	24.9 (13.8-44.9)	1/11 (10)
All ages	1097.0	408	37.2 (33.8-41.0)	478	43.6 (39.8-47.7)	70/478 (15)

	Any illness ≥1 symptom (%)		≥2 symptoms (any)(%)		ILI (Fever and cough)(%)	
	N[c](%)[d]	Rate (95% CI)	N[c](%)[d]	Rate (95% CI)	N[c](%)[d]	Rate (95% CI)
<1	11 (79)	52.1 (28.9-94.1)	8 (57)	37.9 (19.0-75.8)	4 (30)	18.9 (7.1-50.5)
1-4	77 (73)	49.6 (39.6-62.0)	51 (49)	32.8 (25.0-43.2)	27 (26)	17.4 (11.9-25.3)
5-12	79 (51)	26.2 (21.0-32.6)	56 (36)	18.5 (14.3-24.1)	28 (18)	9.3 (6.4-13.4)
13-18	42 (60)	26.8 (19.8-36.3)	28 (40)	17.9 (12.3-25.9)	15 (21)	9.6 (5.8-15.9)
19-44	33 (39)	11.7 (8.3-16.4)	28 (33)	9.9 (6.8-14.3)	11 (13)	3.9 (2.2-7.0)
45-64	20 (50)	14.8 (9.6-23.0)	14 (35)	10.4 (6.1-17.5)	7 (18)	5.2 (2.5-10.9)
≥65	6 (55)	13.6 (6.1-30.2)	6 (55)	13.6 (6.1-30.2)	2 (18)	4.5 (1.1-18.1)
All ages	268 (56)	24.4 (21.7-27.5)	191 (40)	17.4 (15.1-20.1)	94 (20)	8.6 (7.0-10.5)

	Medically attended illness ≥1 symptom		≥2 symptom		ILI (Fever and cough)(%)	
	N[c](%)[d]	Rate (95% CI)	N[c](%)[d]	Rate (95% CI)	N[c](%)[d]	Rate (95% CI)
<1	3 (21)	14.2 (4.6-44.1)	3 (21)	14.2 (4.6-44.1)	2 (14)	9.5 (2.4-37.9)
1-4	23 (22)	14.8 (9.8-22.3)	18 (17)	11.6 (7.3-18.4)	7 (7)	4.5 (2.1-9.5)
5-12	21 (14)	7.0 (4.5-10.7)	17 (11)	5.6 (3.5-9.1)	10 (6)	3.3 (1.8-6.2)
13-18	8 (11)	5.1 (2.6-10.2)	5 (7)	3.2 (1.3-7.7)	2 (3)	1.3 (0.3-5.1)
19-44	5 (6)	1.8 (0.7-4.2)	4 (5)	1.4 (0.5-3.8)	2 (2)	0.7 (0.2-2.8)
45-64	4 (10)	3.0 (1.1-7.9)	3 (8)	2.2 (0.7-6.9)	3 (8)	2.2 (0.7-6.9)
≥65	2(18)	4.5 (1.1-18.1)	2 (18)	4.5 (1.1-18.1)	1 (9)	2.3 (0.3-16.1)
All ages	66 (14)	6.0 (4.7-7.7)	52 (11)	4.7 (3.6-6.2)	27 (6)	2.5 (1.7-3.6)

ILI – Influenza-like illness. Incidence rate estimated as number of episodes divided by the person time under observation [a]Individuals testing influenza positive at least once during follow up counted once [b]Includes repeat episodes (Among 569 individuals who experienced at least one influenza episode in a season, 474 (83%) had 1 episode, 91 (16%) had 2 episodes and 4 (1%) had 3 episodes) [c]Number of episodes and percent of influenza infection episodes with ≥1 symptom, ≥2 symptoms or ILI (includes repeat episodes) [d]Percent of all episodes

379 Supplementary table 3: Factors associated with influenza incidence at a rural and an urban site, South Africa, 2017-2018*

		Including repeat influenza episode			Including only first episode		
Variable		**Rate per 100 person seasons [a] (95% CI)**	**Univariate RR**	**Multivariable RR**	**Rate per 100 person seasons [b] (95% CI)**	**Univariate RR**	**Multivariable RR**
Year	2017	43.4 (38.3-49.3)	Reference	Ref	37.6 (32.9-43.1)	Reference	Ref
	2018	43.7 (38.5-49.6)	1.0 (0.8-1.2)	1.0 (0.8-1.2)	36.7 (32.0-42.2)	1.0 (0.8-1.2)	1.0 (0.8-1.2)
Site	Rural	43.8 (38.6-49.6)	Reference	Ref	36.7 (32.0-42.1)	Reference	Ref
	Urban	43.4 (38.2-49.3)	1.0 (0.8-1.2)	1.0 (0.9-1.4)	37.7 (32.8-43.2)	1.0 (0.8-1.2)	1.1 (0.9-1.4)
Age group (years)	<1	66.3 (39.3-112.0)	2.7 (1.2-5.8)	2.7 (1.2-5.7)	47.4 (25.5-88.0)	2.1 (1.0-4.4)	2.1 (1.0-4.3)
	1-4	67.6 (55.8-81.8)	2.7 (1.5-5.1)	2.8 (1.5-5.1)	56.0 (45.4-69.1)	2.5 (1.3-4.5)	2.5 (1.4-4.7)
	5-12	51.2 (43.7-59.9)	2.1 (1.1-3.8)	2.1 (1.1-3.8)	42.9 (36.1-50.9)	1.9 (1.1-3.4)	1.9 (1.1-3.5)
	13-18	44.4 (35.1-56.1)	1.8 (1.0-3.3)	1.8 (1.0-3.3)	37.4 (29.0-48.3)	1.7 (0.9-3.0)	1.7 (0.9-3.0)
	19-44	29.7 (24.0-36.8)	1.2 (0.6-2.2)	1.2 (0.6-2.2)	26.9 (21.5-33.6)	1.2 (0.6-2.2)	1.2 (0.6-2.2)
	45-64	29.7 (21.8-40.4)	1.2 (0.6-2.3)	1.2 (0.6-2.2)	27.4 (19.9-37.9)	1.2 (0.6-2.3)	1.2 (0.6-2.3)
	≥65	24.9 (13.8-44.9)	Reference	Ref	22.6 (12.2-42.0)	Reference	Ref
Sex	Female	42.6 (37.9-47.8)	0.9 (0.8-1.1)		36.8 (32.5-41.7)	1.0 (0.8-1.1)	
	Male	45.1 (39.2-51.9)	Reference		37.8 (32.4-44.1)	Reference	
HIV	Infected	36.2 (28.1-46.8)	0.8 (0.6-1.1)		31.9 (24.3-41.9)	0.8 (0.7-1.1)	
	Uninfected	44.6 (40.4-49.2)	Reference		37.9 (34.1-42.1)	Reference	
Other underlying illness	Absent	43.6 (39.9-47.8)	Reference		37.2 (33.7-41.0)	Reference	

	Present	40.7 (22.6-73.6)	0.9 (0.5-1.7)	37.0 (19.9-68.8)	1.0 (0.6-1.8)
BMI[c]	Underweight	53.9 (40.4-72.0)	1.1 (0.9-1.5)	46.9 (34.4-64.0)	1.2 (0.9-1.5)
	Normal weight	47.6 (42.6-53.2)	Reference	39.8 (35.3-45.0)	Reference
	Overweight	36.9 (28.6-47.5)	0.8 (0.6-1.0)	33.8 (25.9-44.0)	0.8 (0.7-1.1)
	Obese	31.0 (24.1-39.9)	0.7 (0.5-0.8)	26.9 (20.5-35.3)	0.7 (0.5-0.9)
Urine cotinine	No exposure	46.6 (40.6-53.5)	Reference	40.1 (34.6-46.6)	Reference
	Passive	45.5 (39.7-52.1)	1.0 (0.8-1.2)	38.3 (33.0-44.4)	1.0 (0.8-1.1)
	Active	28.2 (21.1-37.6)	0.6 (0.4-0.8)	26.3 (19.5-35.5)	0.7 (0.5-0.9)
Number of individuals in household	3-5	46.0 (40.8-52.0)	Reference	38.6 (33.8-44.1)	Reference
	6-10	41.6 (36.1-48.0)	0.9 (0.7-1.1)	36.2 (31.0-42.1)	0.9 (0.7-1.1)
	≥11	37.0 (25.6-53.6)	0.8 (0.5-1.3)	33.0 (22.3-48.9)	0.8 (0.5-1.3)
Crowding (people/sleeping room)	<2	40.3 (35.1-46.4)	Reference	33.8 (29.1-39.4)	Reference
	≥2	46.2 (41.1-51.9)	1.1 (0.9-1.4)	39.9 (35.2-45.3)	1.2 (1.0-1.4)

*Estimated using Poisson regression adjusted for clustering by site and household.

[a] Includes multiple episodes of influenza infection [b]Includes only the first episode of influenza infection [c]BMI=body mass index calculated using the formula (weight in kilograms)/(height in metres squared). We defined BMI categories as follows: underweight - age <18 years weight for age or BMI <-2 standard deviations of the World Health Organization (WHO) Child Growth Standards, age ≥18 years BMI <18.5kg/m2; overweight - age <18 years BMI >+1 and ≤+2 standard deviations of the WHO growth standards, age ≥18 years BMI ≥25 and <30kg/m2, obese – age <18 years BMI >+2 standard deviations of the WHO growth standards, age ≥18 years BMI ≥30 kg/m2

RR-Rate ratio

Additional variables evaluated but not found to be significant on univariate or multivariable analysis: Influenza vaccination, level of education, employment, use of alcohol, current or previous smoking, current or previous tuberculosis, household income, mean indoor summer and winter respirable particulate matter, mean indoor summer and winter temperature

389 Supplementary table 4: Proportion of individuals seeking care and reporting absenteeism by number of
390 symptoms reported, at a rural and an urban site, South Africa, 2017-2018

Symptoms	**1 symptom**	**≥2 symptoms (no ILI)**	**ILI**	**Any symptom**	
	n/N (%)	**n/N (%)**	**n/N (%)**	**n/N (%)**	**P[b]**
Seeking care	14/77 (18)	25/97 (26)	27/94 (29)	66/268 (25)	0.304
Absenteeism[a]	13/41 (32)	44/67 (66)	38/60 (63)	95/168 (57)	<0.001

391

392 ILI – influenza-like illness [a]Absenteeism estimated among individuals attending school or work [b]Comparing 1
393 symptom, ≥2 symptoms (no ILI) and ILI using Chi squared test

Supplementary table 5: Combinations of type and subtype among individuals with repeat influenza infections within a season, at a rural and an urban site, South Africa, 2017-2018

Combination of type, subtype and lineage	1 episode n=339 (%)	2 episodes n=66 (%)	3 episodes n=3 (%)
A (H3N2)	132 (39)	3 (5)	0
A (H1N1)pdm09	55 (16)	1 (2)	0
B Victoria	107 (32)	5 (8)	0
B Yamagata	45 (13)	1 (2)	0
A(H3N2)/A(H1N1)pdm09	0	2 (3)	0
A(H3N2)/B Victoria	0	1 (2)	0
A(H3N2)/B Yamagata	0	25 (38)	2 (67)
A(H1N1)pdm09/B Victoria	0	28 (42)	1 (33)

Supplementary table 6: Rates of influenza infections per 100 person season by influenza type, subtype or lineage by year and site, at a rural and an urban site, South Africa, 2017-2018[a]

Year	Site	A		A(H3N2)		A(H1N1)pdm09		B		B Victoria		B Yamagata	
		n	Rate[b] (95% CI)	n	Rate[b] (95% CI)	n	Rate[b] (95% CI)	n	Rate[b] (95% CI)	n	Rate[b] (95% CI)	n	Rate[b] (95% CI)
2017-2018	Rural and urban	258	23.5 (20.8-26.6)	169	15.4 (13.2-17.9)	89	8.1 (6.6-10.0)	222	20.2 (17.7-23.1)	147	13.4 (11.4-15.8)	75	6.8 (5.5-8.6)
2017-2018	Rural	150	27.0 (23.0-31.7)	93	16.7 (13.7-20.5)	57	10.3 (7.9-13.3)	93	16.7 (13.7-20.5)	71	12.8 (10.1-16.1)	22	4.0 (2.6-6.0)
2017-2018	Urban	108	19.9 (16.5-24.1)	76	14.0 (11.2-17.6)	32	5.9 (4.2-8.4)	129	23.8 (20.0-28.3)	76	14.0 (11.2-17.6)	53	9.8 (7.5-12.8)
2017	Rural and urban	167	30.2 (26.0-35.2)	166	30.0 (25.8-35.0)	1	0.2 (0.0-1.3)	75	13.6 (10.8-17.0)	0	0	75	13.6 (10.8-17.0)
2017	Rural	91	32.1 (26.2-39.5)	90	31.8 (35.8-39.1)	1	0.4 (0.0-2.5)	22	7.8 (5.1-11.8)	0	0	22	7.8 (5.1-11.8)
2017	Urban	76	28.2 (22.5-35.3)	76	28.2 (22.5-35.3)	0		53	19.7 (15.0-35.8)	0	0	53	19.7 (15.0-25.8)
2018	Rural and urban	91	16.7 (13.6-20.5)	3	0.6 (0.2-1.7)	88	16.2 (13.1-19.9)	147	27.0 (23.0-31.7)	147	27.0 (23.0-31.7)	0	0
2018	Rural	59	21.7 (16.8-28.0)	3	1.1 (0.4-3.4)	56	20.6 (15.8-26.7)	71	26.1 (20.7-32.9)	59	21.5 (16.7-27.7)	0	0
2018	Urban	32	11.7 (8.3-16.6)	0	0	32	11.7 (8.3-16.6)	76	27.9 (22.3-34.9)	76	27.9 (22.3-34.9)	0	0

[a]Includes 2 episodes of mixed infection in 2017 (both A(H3N2)/B Yamagata) [b] Incidence rate estimated as number of episodes divided by the person time under observation

401 Supplementary table 7: Rates of influenza infections and illness per 100 person seasons and percent of all infections by influenza type, subtype or lineage, at a rural and an
402 urban site, South Africa, 2017-2018

Medical attendance	Endpoint	All influenza		Influenza A		Influenza A(H3N2)		Influenza A(H1N1)		Influenza B		Influenza B Yamagata		Influenza B Victoria	
		N (%)	Rate[a] (95% CI)	N (%)	Rate[a] (95% CI)	N (%)	Rate[a] (95% CI)	N (%)	Rate[a] (95% CI)	N (%)	Rate[a] (95% CI)	N (%)	Rate[a] (95% CI)	N (%)	Rate[a] (95% CI)
Overall	Infections	478 (100)	43.6 (39.8-47.7)	258 (100)	23.5 (20.8-26.6)	169 (100)	15.4 (13.2-17.9)	89 (100)	8.1 (6.6-10.0)	222 (100)	20.2 (17.7-23.1)	75 (100)	6.8 (5.5-8.6)	147 (100)	13.4 (11.4-15.8)
	≥1 symptom	260 (54)	23.7 (21.0-26.8)	154 (60)	14.0 (12.0-16.4)	98 (58)	8.9 (7.3-10.9)	56 (63)	5.1 (3.9-6.6)	114 (51)	10.4 (8.6-12.5)	31 (41)	2.8 (2.0-4.0)	83 (56)	7.6 (6.1-9.4)
	≥2 symptoms (any)	190 (40)	17.3 (15.0-20.0)	114 (44)	10.4 (8.6-12.5)	77 (46)	7.0 (5.6-8.8)	37 (42)	3.4 (2.4-4.7)	77 (35)	7.0 (5.6-8.8)	21 (28)	1.9 (1.2-2.9)	56 (38)	5.1 (3.9-6.6)
	ILI (Fever and cough)	93 (19)	8.5 (6.9-18.1)	53 (21)	4.8 (3.7-6.3)	29 (17)	2.6 (1.8-3.8)	24 (27)	2.2 (1.5-3.3)	41 (18)	3.7 (2.8-5.1)	10 (13)	0.9 (0.5-1.7)	31 (21)	2.8 (2.0-4.0)
Medically attended	≥1 symptom	64 (13)	5.8 (4.6-18.1)	45 (17)	4.1 (3.1-5.5)	27 (16)	2.5 (1.7-3.6)	18 (20)	1.6 (1.0-2.6)	21 (9)	1.9 (1.2-2.9)	2 (3)	0.2 (0.0-0.7)	19 (13)	1.7 (1.1-2.7)
	≥2 symptoms (any)	51 (11)	4.6 (3.5-6.1)	37 (14)	3.4 (2.4-4.7)	24 (14)	2.2 (1.5-3.3)	13 (15)	1.2 (0.7-2.0)	15 (7)	1.4 (0.8-2.3)	0 (0)	0.0	15 (10)	1.4 (0.8-2.3)
	ILI (Fever and cough)	26 (5)	2.4 (1.6-3.5)	18 (7)	1.6 (1.0-2.6)	10 (6)	0.9 (0.5-1.7)	8 (9)	0.7 (0.4-1.5)	9 (4)	0.8 (0.4-1.6)	0 (0)	0.0	9 (6)	0.8 (0.4-1.6)

403 CI – confidence interval, N – number of episodes, ILI – Influenza-like illness [a]Incidence rate estimated as number of episodes divided by the person time under observation

404

405 Supplementary table 8: Rates[a] of influenza infections per 100 person seasons by influenza type and subtype and age group, at a rural and an urban site, South Africa, 2017-
406 2018

Age group (years)	Influenza A	Influenza A(H3N2)	Influenza A(H1N1)pdm09	Influenza B	Influenza B Victoria	Influenza B Yamagata
<1	28.4 (12.8-63.3)	14.2 (4.6-44.1)	14.2 (4.6-44.1)	37.9 (19.0-75.8)	37.9 (19.0-75.8)	0.0 (0)
1-4	38.0 (29.4-49.0)	17.4 (11.9-25.3)	20.6 (14.6-29.1)	30.3 (22.7-40.3)	22.5 (16.2-31.4)	7.7 (4.4-13.6)
5-12	25.2 (20.1-31.5)	16.6 (12.5-21.8)	8.6 (5.9-12.6)	25.8 (20.7-32.2)	20.2 (15.7-26.0)	5.6 (3.5-9.1)
13-18	27.5 (20.4-37.0)	21.1 (15.0-29.6)	6.4 (3.4-11.9)	17.9 (12.3-25.9)	6.4 (3.4-11.9)	11.5 (7.2-18.2)
19-44	15.2 (11.3-20.5)	11.7 (8.3-16.4)	3.5 (1.9-6.6)	14.5 (10.7-19.7)	8.5 (5.7-12.7)	6.0 (3.7-9.7)
45-64	17.8 (11.9-26.5)	12.6 (7.8-20.3)	5.2 (2.5-10.9)	11.9 (7.3-19.4)	5.9 (3.0-11.9)	5.9 (3.0-11.9)
≥65	15.8 (7.5-33.2)	13.6 (6.1-30.2)	2.3 (0.3-16.1)	9.0 (3.4-24.1)	2.3 (0.3-16.1)	6.8 (2.2-21.0)

407

408 [a] Incidence rate estimated as number of episodes divided by the person time under observation

409 Supplementary table 9: Factors associated with duration of influenza shedding at a rural and an urban site,
410 South Africa, 2017-2018*

		Shedding duration (days)	Univariate		Multivariable	
Variable		**Mean±SD (Range)**	**HR**	**p**	**aHR**	**p**
Age group (years)	<1	10.6±6.1 (3-22)	0.2 (0.1-0.3)	<0.001	0.2 (0.1-0.5)	<0.001
	1-4	8.7±4.9 (3-24)	0.2 (0.2-0.3)		0.3 (0.2-0.5)	
	5-12	6.6±5.1 (3-31)	0.4 (0.3-0.6)		0.5 (0.3-0.7)	
	13-18	6.5±4.1 (3-19)	0.4 (0.3-0.6)		0.5 (0.3-0.7)	
	19-44	4.6±2.8 (3-16)	Reference		Reference	
	45-64	4.7±3.4 (3-18)	0.8 (0.5-1.3)		0.6 (0.4-1.0)	
	≥65	4.0±1.7 (3-7)	0.9 (0.4-1.9)		0.9 (0.4-1.8)	
Sex	Female	6.3±4.6 (3-31)	0.9 (0.7-1.1)	0.314		
	Male	6.8±4.8 (3-28)	Reference			
HIV	Infected	5.1±3.2 (3-18)	1.8 (1.3-2.6)	<0.001		
	Uninfected	6.8±4.8 (3-18)	Reference			
	Unknown		Not estimated			
Other underlying illness	Absent	6.6±4.7 (3-31)	Reference	0.935		
	Present	6.7±5.5 (3-22)	0.9 (0.5-2.0)			
BMI	Underweight	6.7±3.9 (3-17)	1.1 (0.7-1.6)	<0.001		
	Normal weight	6.9±5.0 (3-31)	Reference			
	Overweight	5.5±3.8 (3-20)	1.7 (1.3-2.4)			
	Obese	5.6±4.1 (3-18)	1.8 (1.3-2.5)			
Symptoms	None	5.1±3.9 (3-21)	Reference	<0.001	Reference	<0.001
	1	7.6±4.9 (3-24)	0.5 (0.3-0.7)		0.6 (0.4-0.9)	
	≥2	7.8±5.0 (3-31)	0.5 (0.4-0.6)		0.6 (0.5-0.8)	
Minimum Ct value	<30	7.7±4.9 (3-31)	0.2 (0.2-0.3)	<0.001	0.3 (0.2-0.4)	<0.001
	≥30	3.8±2.3 (3-17)	Reference		Reference	
Subtype	A(H3N2)	6.3±4.2 (3-31)	1.0 (0.7-1.4)	0.448		
	A(H1N1)pdm09	6.4±4.4 (3-20)	1.1 (0.8-1.6)			
	B Victoria	7.1±5.2 (3-24)	0.9 (0.8-1.6)			
	B Yamagata	6.5±4.9 (3-28)	Reference			

411 SD – Standard deviation, HR – Hazard ratio *Estimated using Weibull accelerated failure time regression
412 adjusted for clustering by site and household. Hazard ration <1 corresponds to prolonged duration of
413 shedding. Samples were collected at 3 to 4 day intervals hence values of 3 days represent a single positive
414 swab.

415 Additional variables evaluated but found not to be associated with duration of symptoms include year, site,
416 influenza vaccination status

Supplementary table 10: Factors associated with serial interval among 109 individuals with interval <12 days at a rural and an urban site, South Africa, 2017-2018[a]

Variable		Interval (days) Mean±SD (Range)	Univariate HR	p	Multivariable aHR	p
Characteristics of the index case						
Age group (years)	<1	7.0±5.7 (3-11)	0.3 (0.1-1.3)	0.051	0.1 (0.0-0.4)	<0.001
	1-4	5.5±2.4 (3-11)	0.6 (0.3-1.2)		0.6 (0.3-1.2)	
	5-12	6.3±3.0 (2-11)	0.4 (0.2-0.8)		0.4 (0.2-0.8)	
	13-18	4.6±1.9 (3-9)	Reference		Reference	
	19-44	5.5±2.9 (3-11)	0.6 (0.3-1.3)		1.2 (0.5-2.9)	
	45-64	7.0±2.0 (4-8)	0.4 (0.1-1.3)		0.8 (0.2-2.7)	
	≥65	3.5±0.7 (3-4)	2.5 (0.6-11.3)		7.9 (1.6-40.0)	
Sex	Female	5.8±2.7 (2-11)	0.9 (0.6-1.5)	0.668		
	Male	5.6±2.6 (2-11)	Reference			
HIV	Infected	5.9±2.7 (3-11)	1.1 (0.4-2.7)	0.916		
	Uninfected	5.7±2.6 (2-11)	Reference			
Number of symptoms	0	6.8±2.7 (2-11)	Reference	0.074	Reference	0.009
	1	5.8±2.5 (3-11)	1.5 (0.6-3.6)		1.6 (0.8-3.5)	
	≥2	5.2±2.2 (2-11)	2.2 (1.1-4.2)		2.2 (1.3-3.8)	
Subtype/Lineage	A(H3N2)	4.8±2.3 (2-11)	Reference	0.017		
	A(H1N1)pdm09	4.8±1.9 (3-9)	1.1 (0.6-2.1)			
	B Victoria	6.1±2.7 (2-11)	0.6 (0.3-1.0)			
	B Yamagata	7.8±2.6 (2-11)	0.3 (0.1-0.7)			
Minimum Ct value	<30	5.5±2.6 (2-11)	1.5 (0.8-2.6)	0.194		
	≥30	6.8±2.7 (3-11)	Reference			
Characteristics of the household member						
Age group (years)	<1	3.0±0.6 (2-4)	11.4 (3.8-33.7)	<0.001	12.9 (4.0-40.9)	<0.001
	1-4	5.5±2.2 (2-10)	1.9 (0.8-4.2)		1.8 (0.8-4.3)	
	5-12	6.3±3.0 (2-11)	1.2 (0.5-2.6)		0.9 (0.4-2.2)	
	13-18	7.0±2.9 (3-11)	Reference		Reference	
	19-44	5.8±2.3 (2-11)	1.6 (0.7-3.5)		1.6 (0.7-3.6)	
	45-64	4.6±2.6 (2-11)	2.3 (0.9-5.9)		3.8 (1.3-11.0)	

	≥65	10.0 (10-10)	0.5 (0.1-4.1)		0.3 (0.0-2.5)
Sex	Female	5.6±2.5 (2-11)	1.1 (0.7-1.8)	0.619	
	Male	5.8±2.8 (2-11)	Ref		
HIV	Infected	5.9±2.8 (2-11)	0.9 (0.5-1.5)	0.709	
	Uninfected	5.7±2.6 (2-11)	Reference		

SD – Standard deviation [a]Estimated using Weibull accelerated failure time regression adjusted for clustering by site and household. Individuals with interval <12 days (n=109) included in the analysis. Samples were collected at 2 to 4 day intervals. Serial interval refers to the interval between first positive influenza result in the index case and the secondary case. Overall mean interval 5.7 days (range 2-11 days), data for 2016 not included as symptom data not available.

Additional factors evaluated but not found to be statistically significant include year, site, employment of index or contact, education level of index or contact, alcohol or smoking of index or contact, urine cotinine level of index or contact, underlying tuberculosis, other underlying illness of index, body mass index of index or household contact, receipt of influenza vaccine of index or contact, duration of shedding of index case, number of people in household, number of rooms, crowding, smoking inside the house, mean indoor summer and winter temperature, mean indoor summer and winter particulate matter.

Supplementary table 11: Factors associated with serial interval among 86 individuals with interval <8 days at a rural and an urban site, South Africa, 2017-2018[a]

Variable		Interval (days) Mean±SD (Range)	Univariate HR	p	Multivariable aHR	p
Characteristics of the index case						
Age group (years)	<1	3.0±0.0 (3-3)	4.9 (0.5-45.7)	0.183	8.9 (0.7-115.2)	0.088
	1-4	4.7±1.7 (3-7)	0.8 (0.4-1.6)		0.7 (0.3-1.6)	
	5-12	5.0±2.2 (2-7)	0.6 (0.3-1.2)		0.5 (0.3-1.6)	
	13-18	4.3±1.4 (3-7)	Reference		Reference	
	19-44	4.3±1.3 (3-7)	1.2 (0.4-3.4)		1.6 (0.5-5.3)	
	45-64	4.0±0.0 (4-4)	1.7 (0.2-15.0)		1.4 (0.1-14.8)	
	≥65	3.5±0.7 (3-4)	2.5 (0.5-12.7)		4.3 (0.7-27.8)	
Sex	Female	4.7±1.8 (2-7)	0.8 (0.5-1.5)	0.536		
	Male	4.6±1.8 (2-7)	Reference			
HIV	Infected	5.1±1.9 (3-7)	0.7 (0.3-1.9)	0.481		
	Uninfected	4.6±1.8 (2-7)	Reference			
Number of symptoms	0	5.0±1.9 (2-7)	Reference	0.145	Reference	0.081
	1	5.0±1.8 (3-7)	0.9 (0.3-2.6)		1.4 (0.5-3.8)	
	≥2	4.5±1.7 (2-7)	1.8 (0.8-3.9)		2.2 (1.0-4.6)	
Subtype/Lineage	A(H3N2)	4.3±1.7 (2-7)	Reference	0.394		
	A(H1N1)pdm09	4.6±1.7 (3-7)	1.0 (0.4-2.0)			
	B Victoria	4.9±1.9 (2-7)	0.7 (0.4-1.4)			
	B Yamagata	5.6±2.0 (2-7)	0.4 (0.2-1.2)			
Minimum Ct value	<30	4.5±1.7 (2-7)	1.5 (0.7-3.3)	0.292		
	≥30	5.6±1.8 (3-7)	Reference			
Characteristics of the household contact						
Age group (years)	<1	3.0±0.6 (3-4)	7.6 (1.6-36.7)	0.004	12.5 (2.4-64.0)	0.001
	1-4	4.9±1.7 (2-7)	1.2 (0.3-4.5)		1.6 (0.4-6.1)	
	5-12	4.8±1.9 (2-7)	1.2 (0.3-4.5)		1.3 (0.3-5.2)	
	13-18	4.8±2.0 (3-7)	Reference		Reference	
	19-44	5.1±1.8 (2-7)	0.9 (0.2-3.0)		1.0 (0.3-3.7)	
	45-64	3.9±1.4 (2-7)	2.3 (0.6-10.0)		2.7 (0.6-10.9)	

	≥65	NE	NE		NE
Sex	Female	4.8±1.8 (2-7)	0.7 (0.4-1.1)	0.128	
	Male	4.3±1.5 (2-7)	Reference		
HIV	Infected	4.8±1.8 (2-7)	0.8 (0.4-1.7)	0.578	
	Uninfected	4.7±1.8 (2-7)	Reference		

SD – Standard deviation, NE – not estimated [a]Estimated using Weibull accelerated failure time regression adjusted for clustering by site and household. Individuals with interval <8 days (n=86) included in the analysis. Samples were collected at 2 to 4 day intervals. Serial interval refers to the interval between first positive influenza result in the index case and the secondary case. Overall mean interval 4.7 days (range 2-7 days), data for 2016 not included as symptom data not available.

Additional factors evaluated but not found to be statistically significant include year, site, employment of index or contact, education level of index or contact, alcohol or smoking of index or contact, urine cotinine level of index or contact, underlying tuberculosis, other underlying illness of index, body mass index of index or household contact, receipt of influenza vaccine of index or contact, duration of shedding of index case, number of people in household, number of rooms, crowding, smoking inside the house, mean indoor summer and winter temperature, mean indoor summer and winter particulate matter.

Supplementary table 12: Factors associated with household cumulative infection risk (HCIR)[a] including all subsequent cases within a household irrespective of serial interval at a rural and an urban site, South Africa, 2017-2018[b]

Variable		HCIR n/N (%, 95% CI)	Univariate OR	p	Multivariable aOR	p
Characteristics of the index case						
Age group (years)	<1	2/13 (15, 2-45)	2.6 (0.3-21.6)	0.008	2.1 (0.2-18.6)	0.078
	1-4	47/256 (18, 14-23)	4.9 (2.0-11.9)		3.5 (1.4-8.9)	
	5-12	50/365 (14, 10-18)	3.3 (1.3-8.0)		3.5 (1.4-9.0)	
	13-18	15/214 (7, 4-11)	Reference		Reference	
	19-44	11/155 (7, 4-12)	1.6 (0.6-4.7)		2.7 (0.9-8.6)	
	45-64	4/80 (5, 1-12)	0.7 (0.2-2.9)		0.9 (0.2-4.0)	
	≥65	4/26 (15, 4-35)	2.3 (0.3-16.1)		3.8 (0.5-29.1)	
Sex	Female	50/429 (12, 9-15)	1.4 (0.8-2.4)	0.223		
	Male	83/683 (12, 10-15)	Reference			
HIV	Infected	8/98 (8, 4-15)	0.8 (0.3-2.1)	0.640		
	Uninfected	124/983 (13, 11-15)	Reference			
Number of symptoms	0	41/521 (8, 6-11)	Reference	<0.001	Reference	0.009
	1	15/186 (8, 5-13)	0.8 (0.4-1.9)		0.4 (0.2-1.1)	
	≥2	77/405 (19, 15-23)	2.9 (1.7-5.3)		1.6 (0.8-3.0)	
Duration of episode (days)	<4	22/562 (4, 2-6)	Reference	<0.001	Reference	<0.001
	4-10	66/366 (18, 14-22)	6.9 (3.6-13.3)		8.6 (4.0-18.3)	
	>10	43/172 (25, 19-32)	7.9 (3.8-16.0)		8.8 (3.8-20.3)	
Subtype/Lineage	A(H3N2)	54/471 (11, 9-15)	1.4 (0.7-2.7)	0.087		
	A(H1N1)pdm09	25/231 (11, 7-16)	1.1 (0.5-2.6)			
	B Victoria	53/302 (18, 13-22)	2.2 (1.0-4.8)			
	B Yamagata	19/202 (9, 7-14)	Reference			
Minimum Ct value	<30	113/701 (16, 13-19)	7.2 (3.5-15.0)	<0.001		
	≥30	18/399 (5, 3-7)	Reference			
Characteristics of the household member						
Age group (years)	<1	7/20 (35, 15-59)	10.9 (2.8-42.9)	0.006	28.9 (6.2-135.7)	<0.001
	1-4	26/163 (16, 11-22)	2.9 (1.3-6.6)		6.5 (2.5-17.0)	

	5-12	45/325 (14, 10-18)	2.1 (1.0-4.5)		3.4 (2.5-17.1)
	13-18	13/166 (8, 4-13)	Reference		Reference
	19-44	41/320 (13, 9-17)	1.7 (0.8-3.6)		2.6 (1.1-6.1)
	45-64	17/167 (10, 6-16)	1.3 (0.6-3.2)		2.0 (0.7-5.3)
	≥65	2/45 (4, 1-15)	0.6 (0.1-3.3)		1.2 (0.2-7.4)
Sex	Female	98/731 (13, 11-16)	1.2 (0.8-1.8)	0.422	
	Male	53/475 (11, 8-14)	Reference		
HIV	Infected	29/185 (16, 11-22)	1.3 (0.7-2.2)	0.388	
	Uninfected	118/982 (12, 10-14)	Reference		
Other underlying illness	Absent	145/1182 (12, 10-14)	Reference	0.508	
	Present	6/24 (25, 10-47)	1.5 (0.5-4.9)		

[a]Number of infections following pathogen introduction into a household [b] Estimated using logistic regression adjusted for clustering by site and household

Additional factors evaluated but not found to be statistically significant include year, site, employment of index or contact, education level of index or contact, alcohol or smoking of index or contact, urine cotinine level of index or contact, underlying tuberculosis, other underlying illness of index, body mass index of index or household contact, receipt of influenza vaccine of index or contact, number of people in household, number of rooms, crowding, smoking inside the house, mean indoor summer and winter temperature, mean indoor summer and winter particulate matter.

454 Supplementary table 13: Factors associated with household cumulative infection risk (HCIR)[a] including
455 subsequent cases within a household with serial interval <8 days at a rural and an urban site, South Africa,
456 2017-2018[b]

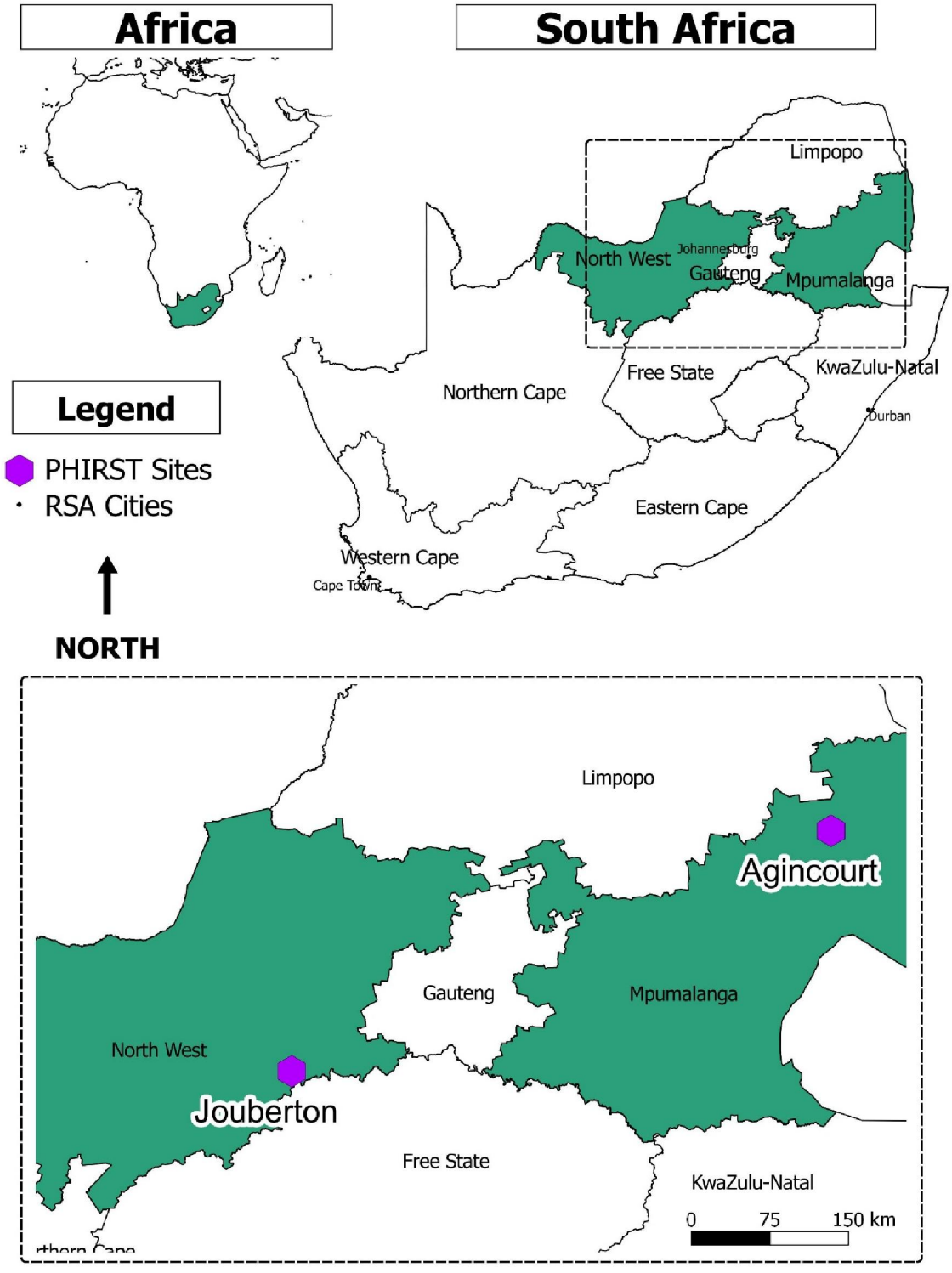
Variable		HCIR % (n/N)	Univariate OR	p	Multivariable aOR	p
Characteristics of the index case						
Age group (years)	<1	1/12 (8)	0.9 (0.1-12.4)	0.006	0.7 (0.1-9.9)	0.003
	1-4	34/246 (14)	3.1 (1.2-7.7)		2.2 (0.9-5.8)	
	5-12	27/342 (8)	1.5 (0.6-3.8)		1.6 (0.6-4.0)	
	13-18	13/212 (6)	Reference		Reference	
	19-44	8/152 (5)	1.0 (0.3-3.1)		1.7 (0.5-5.6)	
	45-64	1/77 (1)	0.2 (0.1-1.8)		0.2 (0.1-2.1)	
	≥65	2/24 (8)	1.6 (0.2-13.2)		2.0 (0.2-19.7)	
Sex	Female	54/654 (8)	1.4 (0.8-2.6)	0.291		
	Male	32/411 (8)	Reference			
HIV	Infected	7/97 (7)	1.2 (0.4-3.2)	0.787		
	Uninfected	78/937 (8)	Reference			
Number of symptoms	0	17/497 (3)	Reference	<0.001	Reference	<0.001
	1	10/181 (6)	1.4 (0.6-3.6)		0.8 (0.3-2.4)	
	≥2	59/387 (15)	5.5 (2.8-11.1)		3.4 (1.6-7.2)	
Duration of episode (days)	<4	12/552 (2)	Reference	<0.001	Reference	<0.001
	4-10	45/345 (13)	7.9 (3.7-16.8)		8.2 (3.4-19.6)	
	>10	28/157 (18)	8.3 (3.6-19.2)		7.0 (2.6-18.6)	
Subtype/Lineage	A(H3N2)	43/460 (9)	3.0 (1.2-7.4)	0.026		
	A(H1N1)pdm09	20/226 (9)	2.2 (0.8-6.3)			
	B Victoria	34/283 (12)	3.7 (1.4-10.3)			
	B Yamagata	7/190 (4)	Reference			
Minimum Ct value	<30	75/663 (11)	7.0 (3.1-15.7)	<0.001		
	≥30	10/331 (3)	Reference			
Characteristics of the household member						
Age group (years)	<1	7/20 (35)	19.4 (4.5-84.3)	<0.001	78.7 (13.3-464.5)	<0.001
	1-4	22/159 (14)	4.4 (1.6-11.7)		13.7 (3.8-48.7)	
	5-12	30/310 (10)	2.5 (1.0-6.3)		4.7 (1.4-15.6)	

	13-18	7/160 (4)	Reference		Reference
	19-44	29/308 (9)	2.2 (0.9-5.7)		4.6 (1.4-14.9)
	45-64	9/159 (6)	1.4 (0.4-4.1)		2.8 (0.8-10.5)
	≥65	0/43 (0)	NE		NE
Sex	Female	70/703 (10)	1.4 (0.8-2.2)	0.203	
	Male	34/456 (7)	Reference		
HIV	Infected	18/174 (10)	1.2 (0.6-2.3)	0.548	
	Uninfected	83/947 (9)	Reference		
Other underlying illness	Absent	101/1138 (9)	Reference	0.926	
	Present	3/21 (14)	0.9 (0.2-4.4)		

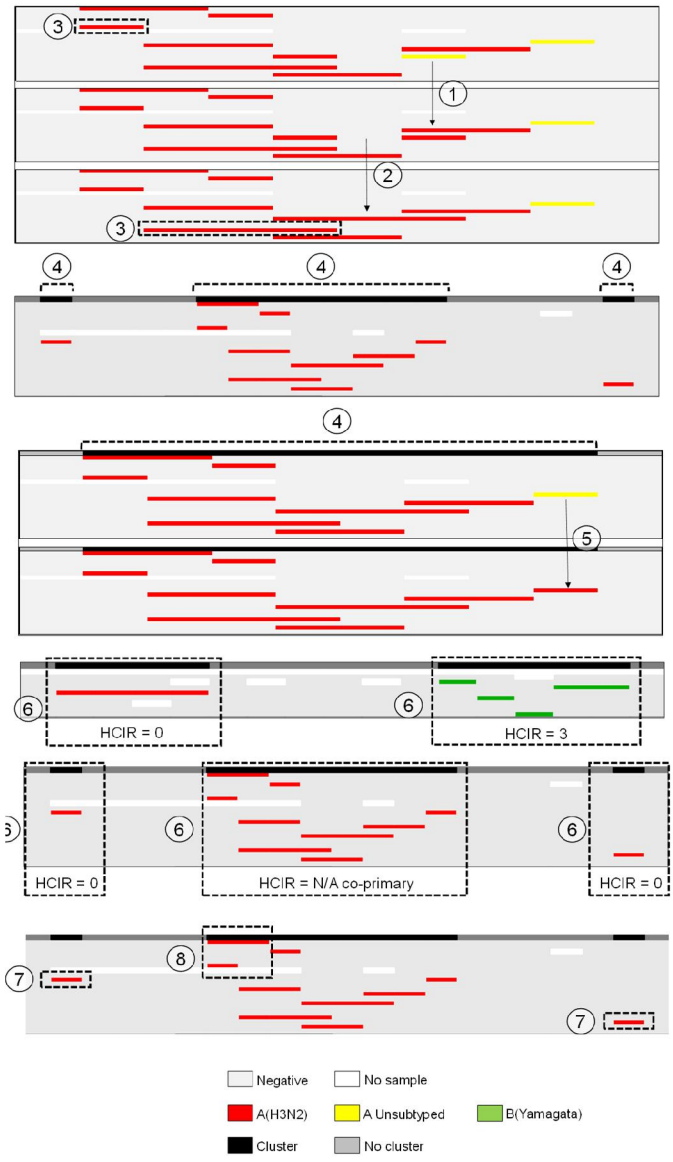
[a] Number of infections following pathogen introduction into a household [b]Estimated using logistic regression adjusted for clustering by site and household

Additional factors evaluated but not found to be statistically significant include year, site, employment of index or contact, education level of index or contact, alcohol or smoking of index or contact, urine cotinine level of index or contact, underlying tuberculosis, other underlying illness of index, body mass index of index or household contact, receipt of influenza vaccine of index or contact, number of people in household, number of rooms, crowding, smoking inside the house, mean indoor summer and winter temperature, mean indoor summer and winter particulate matter.

Supplementary figure 1: Location of rural (Agincourt) and urban (Jouberton) study sites in South Africa



468 Supplementary figure 2



1. For real-time reverse transcription polymerase chain reaction (rRTPCR) positivity where subtype or lineage was not determined we assigned a subtype or lineage if the individual had a confirmed subtype or lineage of the same influenza type (A or B) within two preceding or following follow-up visits. Example, influenza A unsubtyped assigned to influenza A(H3N2) based on influenza A(H3N2) positivity two visits prior

2. We considered a new infection of the same subtype or lineage in the same individual when the individual tested positive for the same subtype >2 weeks of the last day of previous positivity; else we considered it a positivity from the same infection episode. Example, two positive influenza A(H3N2) swabs with a negative swab between updated to influenza A(H3N2).

3. We defined an influenza infection episode as at least one nasopharyngeal swab rRTPCR positive for influenza. Episode duration was estimated from the first to the last day of influenza rRTPCR positivity with the same type/subtype/lineage.

4. A cluster was composed of all infections of the same subtype and lineage within a household within an interval between infections of ≤2 mean serial intervals (3.5 days) including single infections within a household. Cluster duration was estimated as the interval from the first day of positivity of the first individual in a cluster to the last day of influenza positivity of the last individual. Examples of clusters of different durations.

5. For rRTPCR positivity where subtype or lineage was not determined we assigned a subtype or lineage if the individual was part of a household cluster. Example, influenza A unsubtyped assigned to influenza A(H3N2) based on influenza A(H3N2) positivity within household for cluster

6. The household cumulative infection risk (HCIR) was defined as the number of subsequent infections within a household cluster following influenza introduction into the household.

7. The primary/index case was defined as the first individual testing positive within a cluster.

8. If two individuals tested positive in the same visit at the start of the cluster they were defined as co-primary cases and not included in the analysis of HCIR.

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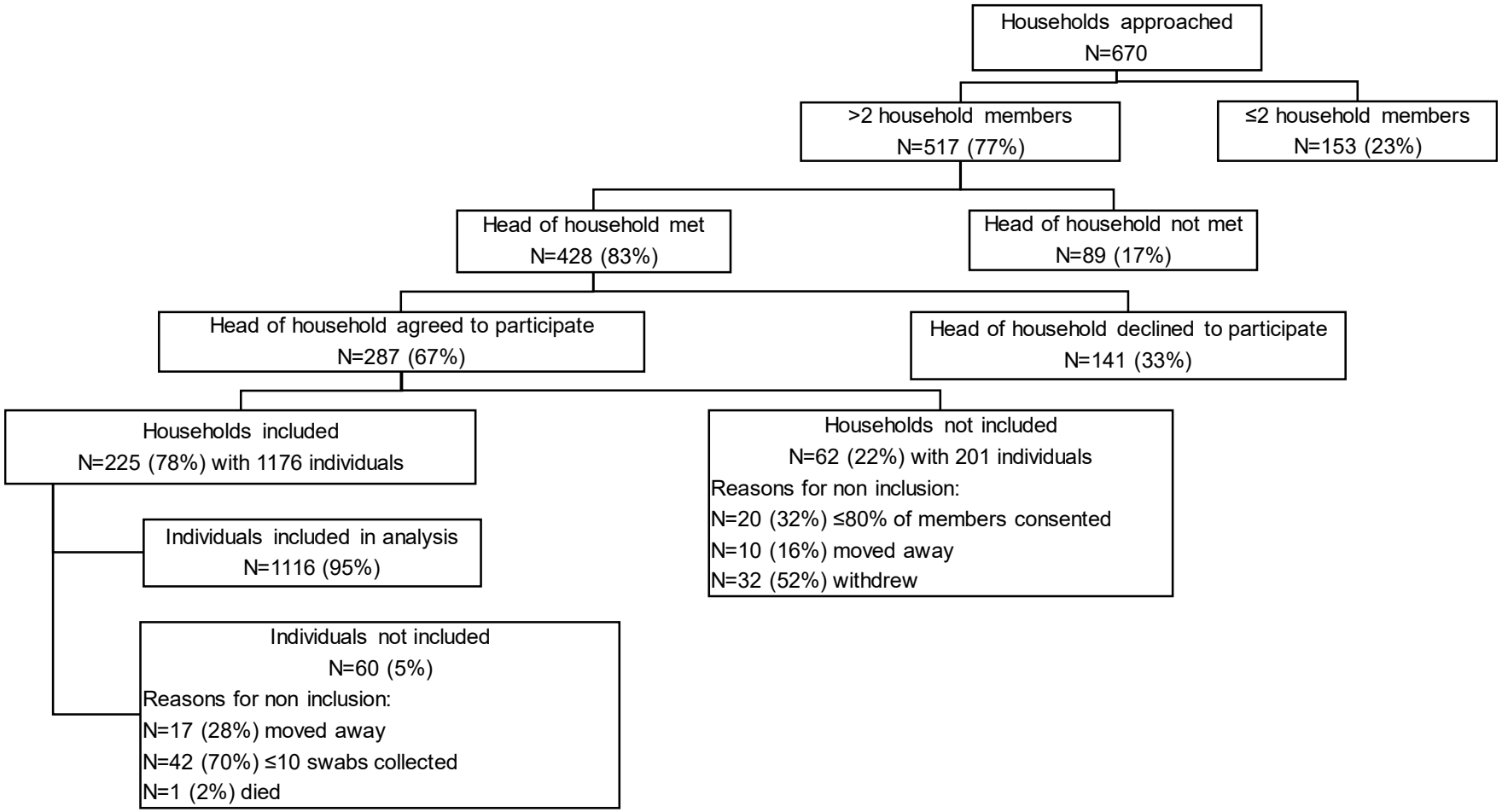
472 Supplementary figure 3: Flow chart of individuals included in the study, an urban and a rural site, South Africa, 2017-2018*



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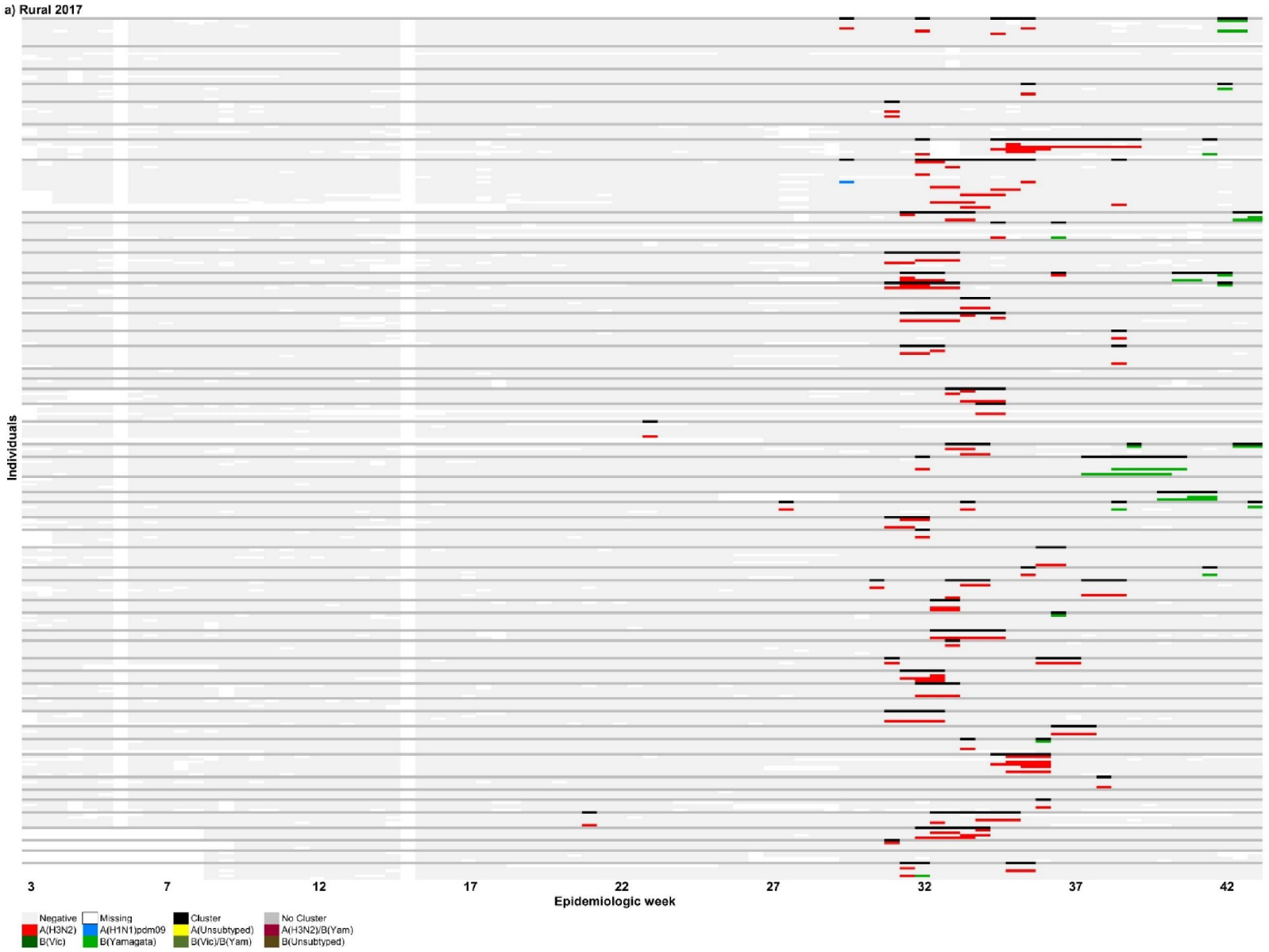
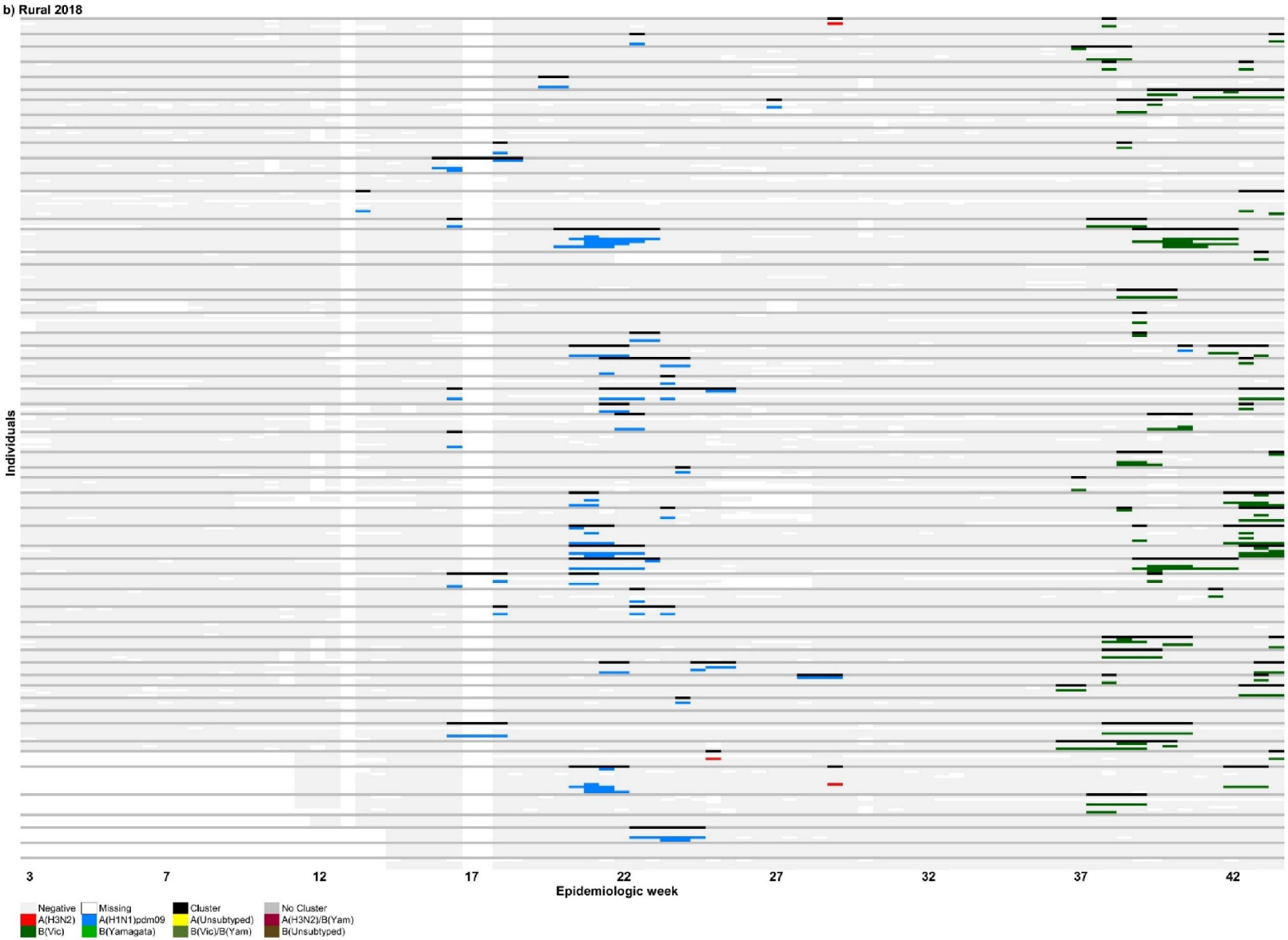
475 * Of 1116 individuals and 225 households included in the analysis, 108 (48%) households and 558 (50%) individuals were enrolled and followed up with twice-weekly
476 swabbing in 2017 and 117 (52%) households and 558 (50%) individuals in 2018

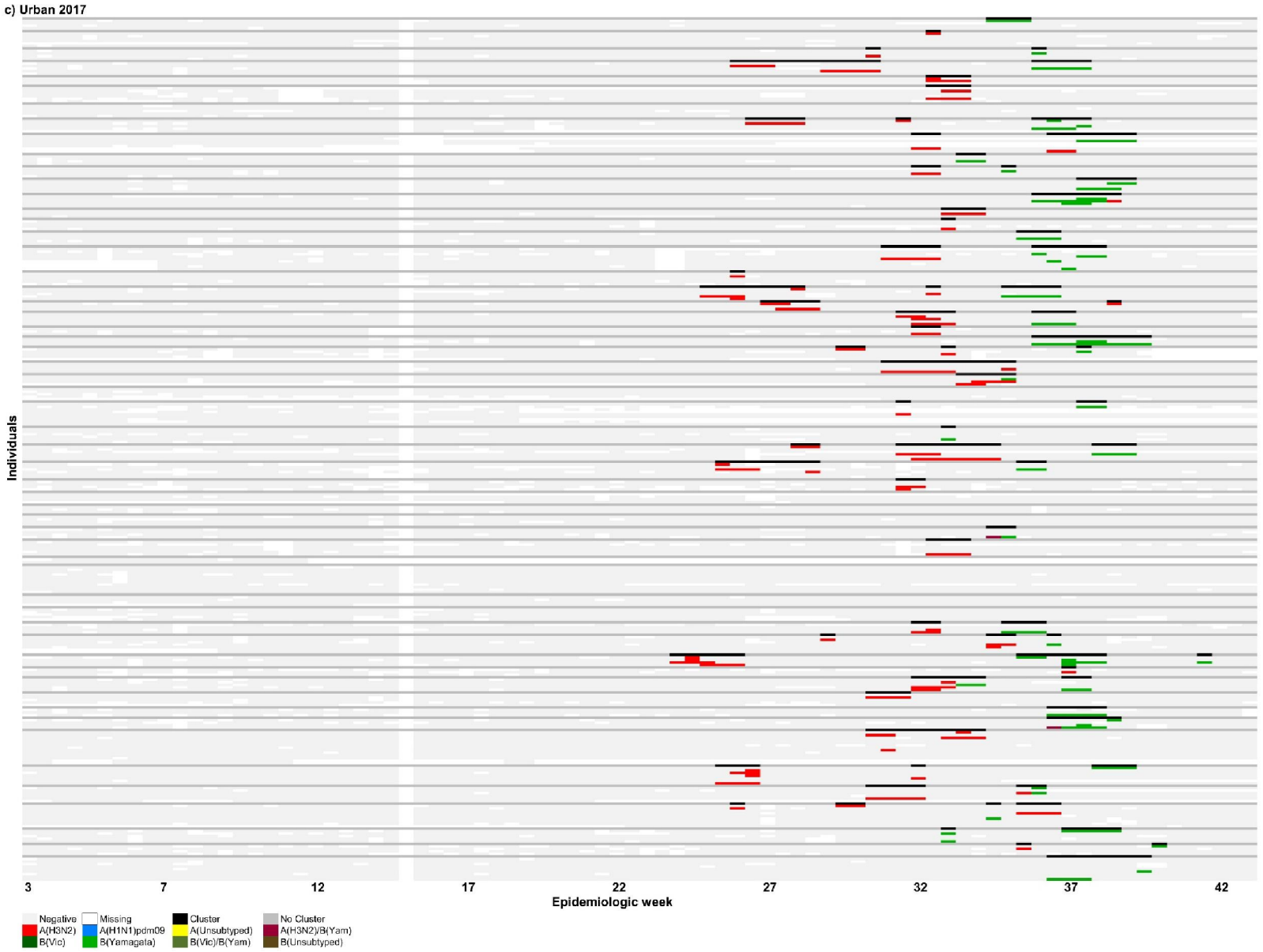
Supplementary figure 4: Influenza detection among study participants, and allocated clusters of infection rural site (a-b) and urban site (c-d) in 2017-2018. Columns are individual follow up visits and rows are individual participants. Each house is separated by a dark grey line on which clusters of infection are shaded black. The white, light grey and coloured horizontal lines each denote an individual with in a household. Each column indicates an individual follow up visit. Follow up visits are coloured white if no sample was tested, light grey if the sample tested negative for influenza and coloured according to the different influenza types and subtypes indicated in the legend if the nasopharyngeal swab tested positive for influenza. A high resolution version of this figure has been provided separately.

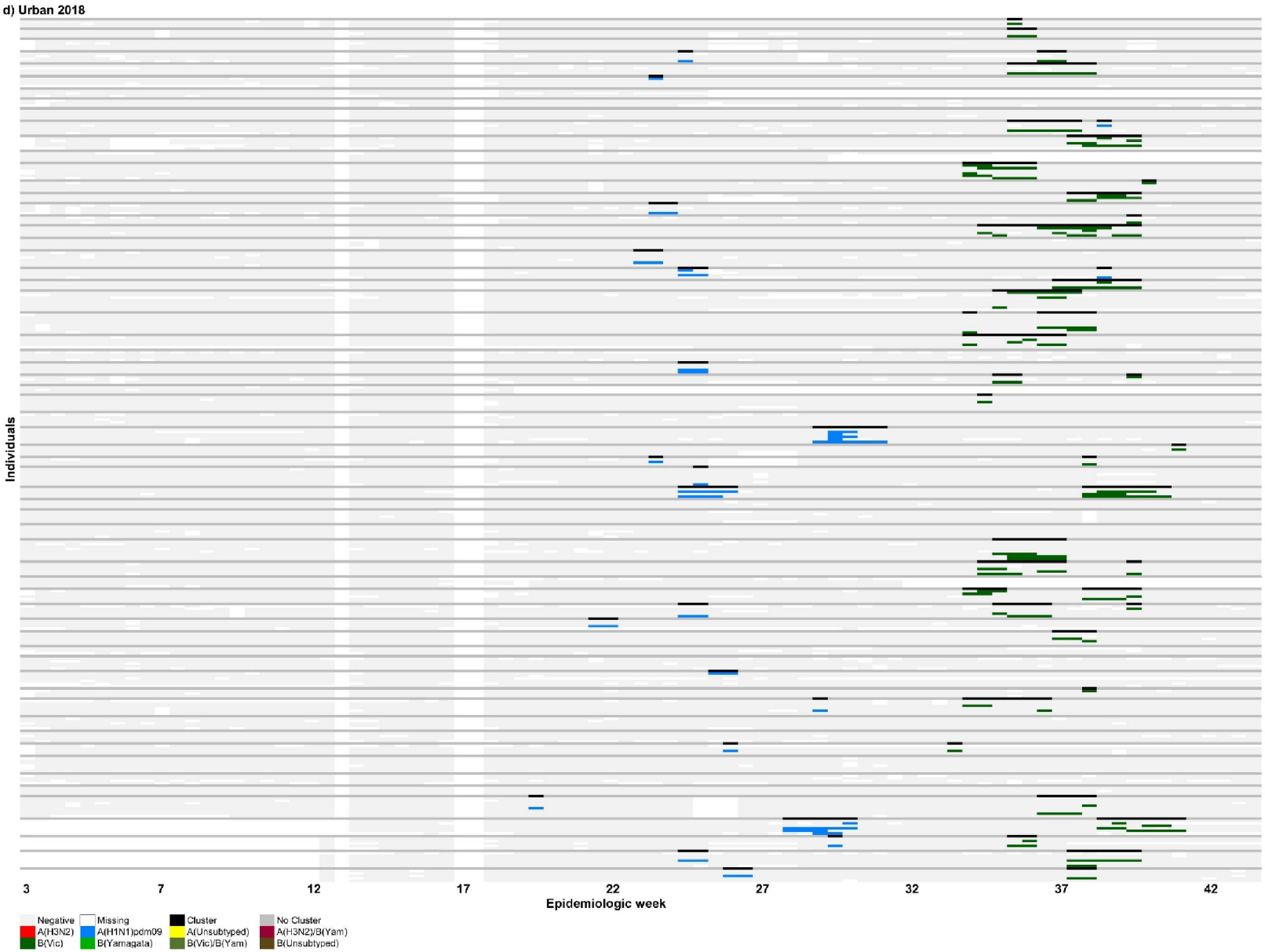

a) Rural 2017
Individuals
3
7
12
17
22
27
32
37
42
Epidemiologic week
Negative
A(H3N2)
B(Vic)
Missing
A(H1N1)pdm09
B(Yamagata)
Cluster
A(Unsubtyped)
B(Vic)/B(Yam)
No Cluster
A(H3N2)/B(Yam)
B(Unsubtyped)

482


b) Rural 2018
Individuals
3
7
12
17
22
27
32
37
42
Epidemiologic week
Negative
A(H3N2)
B(Vic)
Missing
A(H1N1)pdm09
B(Yamagata)
Cluster
A(Unsubtyped)
B(Vic)/B(Yam)
No Cluster
A(H3N2)/B(Yam)
B(Unsubtyped)

483


c) Urban 2017
Individuals
3
7
12
17
22
27
32
37
42
Epidemiologic week
Negative
A(H3N2)
B(Vic)
Missing
A(H1N1)pdm09
B(Yamagata)
Cluster
A(Unsubtyped)
B(Vic)/B(Yam)
No Cluster
A(H3N2)/B(Yam)
B(Unsubtyped)


d) Urban 2018
Individuals
3
7
12
17
22
27
32
37
42
Epidemiologic week
Negative
A(H3N2)
B(Vic)
Missing
A(H1N1)pdm09
B(Yamagata)
Cluster
A(Unsubtyped)
B(Vic)/B(Yam)
No Cluster
A(H3N2)/B(Yam)
B(Unsubtyped)

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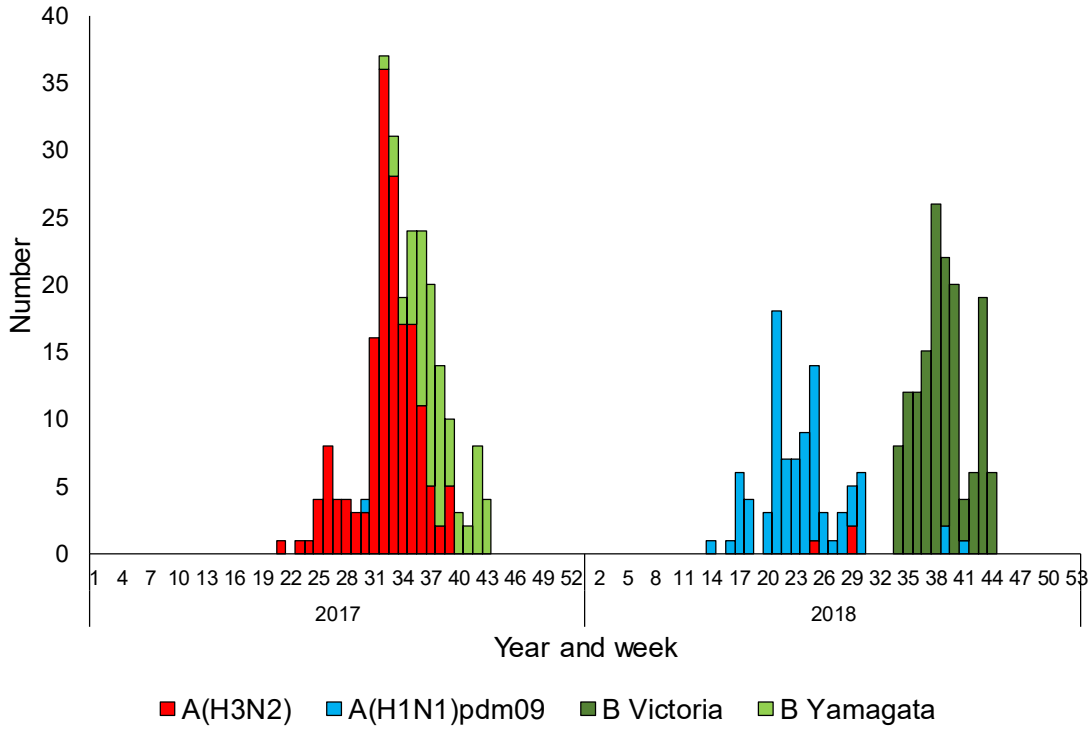
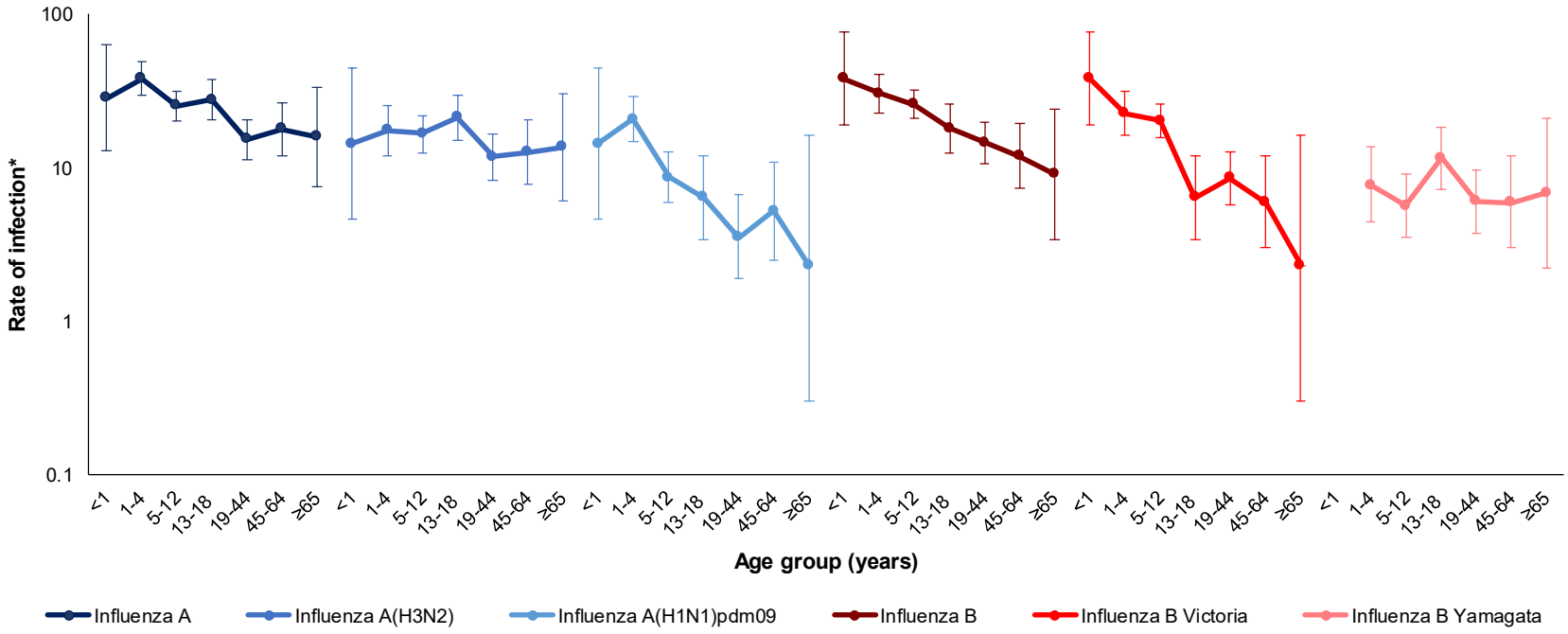
Supplementary figure 5: Epidemic curve of influenza types, subtypes and lineages by year at a rural and an urban site, South Africa, 2017-2018



Supplementary figure 6: Rates of influenza infections per 100 person seasons by age group, type, subtype and lineage, at a rural and an urban site, South Africa, 2017-2018



*Axis plotted on log scale

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