Asymptomatic transmission and high community burden of seasonal influenza in an urban and a rural community in South Africa, 2017–18 (PHIRST): a population cohort study

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Summary

Background Data on influenza community burden and transmission are important to plan interventions especially in resource-limited settings. However, data are limited, particularly from low-income and middle-income countries. We aimed to evaluate the community burden and transmission of influenza in a rural and an urban setting in South Africa.

Methods In this prospective cohort study approximately 50 households were selected sequentially from both a rural setting (Agincourt, Mpumalanga Province, South Africa; with a health and sociodemographic surveillance system) and an urban setting (Klerksdorp, Northwest Province, South Africa; using global positioning system data), enrolled, and followed up for 10 months in 2017 and 2018. Different households were enrolled in each year. Households of more than two individuals in which 80% or more of the occupants agreed to participate were included in the study. Nasopharyngeal swabs were collected twice per week from participating household members irrespective of symptoms and tested for influenza using real-time RT-PCR. The primary outcome was the incidence of influenza infection, defined as the number of real-time RT-PCR-positive episodes divided by the person-time under observation. Household cumulative infection risk (HCIR) was defined as the number of subsequent infections within a household following influenza introduction.

Findings 81 430 nasopharyngeal samples were collected from 1116 participants in 225 households (follow-up rate 88%). 917 (1%) tested positive for influenza; 178 (79%) of 225 households had one or more influenza-positive individual. The incidence of influenza infection was 43·6 (95% CI 39·8–47·7) per 100 person-seasons. 69 (17%) of 408 individuals who had one influenza infection had a repeat influenza infection during the same season. The incidence (67·4 per 100 person-seasons) and proportion with repeat infections (22 [23%] of 97 children) were highest in children younger than 5 years and decreased with increasing age (p<0·0001). Overall, 268 (56%) of 478 infections were symptomatic and 66 (14%) of 478 infections were medically attended. The overall HCIR was 10% (109 of 1088 exposed household members infected [95% CI 9–13%). Transmission (HCIR) from index cases was highest in participants aged 1–4 years (16%; 40 of 252 exposed household members) and individuals with two or more symptoms (17%; 68 of 396 exposed household members). Individuals with asymptomatic influenza transmitted infection to 29 (6%) of 509 household contacts. HIV infection, affecting 167 (16%) of 1075 individuals, was not associated with increased incidence or HCIR.

Interpretation Approximately half of influenza infections were symptomatic, with asymptomatic individuals transmitting influenza to 6% of household contacts. This suggests that strategies, such as quarantine and isolation, might be ineffective to control influenza. Vaccination of children, with the aim of reducing influenza transmission might be effective in African settings given the young population and high influenza burden.

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Introduction

Seasonal influenza causes approximately 300 000–600 000 respiratory deaths globally annually, with the highest rates in sub-Saharan Africa.[1] The 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 important to guide the use of non-pharmaceutical interventions and vaccination strategies and might inform pandemic preparedness.[2,3] Accurate disease burden and transmission estimates are particularly relevant in Africa, where access to and quality of care might be restricted. However, data on the community burden and transmission of influenza in Africa are few in number.[1]

The burden of mild influenza illness is higher in younger individuals (<5 years), and more severe illness occurs in extremes of age (<5 years and >60 years) and in individuals with underlying medical conditions, such as HIV.[4–7] In addition to severe illness, milder influenza illness episodes

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See Online for appendix

For the **protocol** see https://www.nicd.ac.za/wp-content/uploads/2021/02/PHIRST-SARS-CoV-2-protocol-V1-amendment-Nov2020-incl-upd-consent.pdf

Research in context

Evidence before this study

Seasonal influenza causes approximately 300 000–600 000 respiratory deaths globally annually, with the highest rates in sub-Saharan Africa. 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 might inform pandemic preparedness. We searched the PubMed database from Jan 1, 2015, to Dec 31, 2019, for research papers, systematic reviews, and meta-analyses with the search terms "influenza" OR "flu" AND "transmission" OR "household transmission" OR "burden" NOT "avian" NOT "swine". A systematic review of the community infection prevalence of influenza found estimates of annual influenza infection rates ranged from 15–35%. A systematic review found that the proportion of influenza virus infections which are symptomatic range from 4–28% and 65–85% from outbreak investigations and serological studies. A systematic review of seasonal influenza household transmission studies found the secondary infection risk for PCR-confirmed influenza in household contacts ranged from 1–38%. Whether asymptomatic individuals can transmit influenza remains an outstanding question.

Added value of this study

We found that on average, 408 (37%) of 1116 individuals were infected at least once with PCR-confirmed influenza each year. Repeat influenza infections within the same season were identified in 69 (17%) of 408 individuals. The resulting incidence of PCR-confirmed influenza infection and illness was 43·6 infections per 100 person-seasons and 24·4 illness episodes per 100 person-seasons and was highest in children younger than 5 years (67·4 infections per 100 person-seasons and 49·9 illness episodes per 100 person-seasons) and decreased with increasing age. Overall, 56% of infections were associated with one or more symptoms. The proportion of symptomatic infections was higher in children younger than 5 years (74% in this age group *vs* 39% in those aged 19–44 years). Overall, there was influenza transmission to 10% of household contacts of an index case. Transmission was highest in children and individuals with two or more symptoms (17%); however, asymptomatic individuals did transmit influenza to 6% of household contacts.

Implications of all the available evidence

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 transmission of influenza to 6% of household contacts by individuals with asymptomatic influenza suggests that asymptomatic individuals might be an important driver of influenza transmission. These data have implications for the use 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.

might be associated with substantial effect on society, including absenteeism and loss of income.[8,9] Studies of household transmission of influenza have identified factors associated with increased susceptibility to infection or probability of onward transmission, including younger age, underlying illness, symptoms, and contact patterns.[10] However, studies of asymptomatic influenza infection are uncommon and usually follow identification of an index case within the household.[11] Estimates of influenza transmission following identification of symptomatic index cases within households might bias the estimation of transmission parameters because asymptomatic or mild cases might have occurred in the household before the enrolment of the index case and the index cases might have more severe illness than those transmitting influenza in the community.[10,12] Studies of influenza burden and transmission that focus on symptomatic illness only are unable to assess the contribution of asymptomatic individuals.

For more on the **Influenza Reagent Resource Program** see www.influenzareagentresource.org

In South Africa, influenza infections cause more than 11 000 deaths and 56 000 hospitalisations annually.[7,9] HIV prevalence was 14% in 2017.[13] Influenza vaccination is recommended for individuals at high risk of severe outcomes—including people older than 65 years, pregnant women, and adults with HIV—but, due to restricted resources, influenza vaccine coverage remains low (<5%).[14] Vaccination strategies targeting community influenza transmitters might be more cost-effective than risk-group based strategies, particularly in settings, such as South Africa, in which vaccination rates and care seeking in high risk groups remain low.[3,7] However, data are needed to understand community burden and transmission dynamics to inform a transmission-based vaccination strategy.

We aimed to address these gaps by evaluating the community burden and transmission of influenza in a rural and an urban setting in South Africa, including the factors associated with infection and transmission, the symptomatic fraction, and the role of asymptomatic illness in transmission.

Methods

Study design and participants

A prospective household observational cohort study of influenza, respiratory syncytial virus and other respiratory pathogens community burden and transmission dynamics in South Africa (PHIRST) was a prospective cohort study done in a rural (Agincourt, Mpumalanga Province, South Africa—nested within a health and

sociodemographic surveillance system [HDSS][15,16]) and an urban (Klerksdorp, North West Province, South Africa) community in South Africa (appendix pp 1, 38). The protocol (appendix p 1) was approved by the University of Witwatersrand, Johannesburg, South Africa, Human Research Ethics Committee and is available online (reference 150808). All participants or their caregivers provided written informed consent.

Households of more than two individuals in which 80% or more of the occupants agreed to participate were included in the study. All household members were eligible for inclusion in the study.

Procedures

In each year of the study (2016–18), we included different households that were consecutively approached until the sample size (110 households) was reached. In the rural setting, households were selected from the HDSS (appendix p 1), and in the urban site households were selected randomly using global positioning system coordinates.

We collected individual baseline data, including demographics and history of underlying illness, from each participant. Cohort participants were followed up twice per week (Monday–Wednesday and Thursday–Saturday) from Jan 15 to Oct 30, 2017, and Jan 15 to Oct 30, 2018. At each visit, irrespective of symptoms, nasopharyngeal swabs were collected and a questionnaire on symptoms, absenteeism, and health-care visits was answered. Field workers were trained in identification of respiratory signs and symptoms. Participants received grocery store vouchers worth US$2·00–2·50 per visit to compensate for the discomfort and time associated with study procedures.

In 2018, we surveyed contact patterns (appendix pp 4–5). Nasopharyngeal samples were collected using nasopharyngeal nylon flocked swabs (PrimeSwab, Longhorn Vaccines & Diagnostics, San Antonio, CA, USA), placed in PrimeStore Molecular Transport Medium (Longhorn Vaccines & Diagnostics) and transported on ice packs to the National Institute for Communicable Diseases, Johannesburg, South Africa, for testing. Nucleic acids were extracted with the Roche MagNA Pure 96 (Roche, Mannheim, Germany) according to the manufacturer's instructions. Nasopharyngeal samples were tested for influenza A and influenza B by real-time RT-PCR using the FTD Flu/RSV detection assay (Fast Track Diagnostics, Luxembourg). Influenza A-positive samples were subtyped using the US Centers for Disease Control and Prevention (CDC) influenza A (H1, H3, or H1pdm09) subtyping kit and influenza B lineage was determined using the CDC B, Yamagata, Victoria lineage typing kit (available through the Influenza Reagent Resource Program).

Participants were considered to have HIV if they ever had a documented positive HIV result or evidence of antiretroviral therapy use; participants were considered

	Overall (n=225)	Rural (n=109)	Urban (n=116)	p
Intensive follow-up year				
2017	108 (48%)	53 (49%)	55 (47%)	1 (ref)
2018	117 (52%)	56 (51%)	61 (53%)	0·86
Number of household members				
3–5	143 (64%)	67 (61%)	76 (66%)	1 (ref)
6–10	72 (32%)	38 (35%)	37 (32%)	0·59
>10	7 (3%)	4 (4%)	3 (3%)	0·60
Median number of household members	5 (3–10)	5 (3–10)	5 (3–10)	0·44
Number of rooms				
1–4	99 (44%)	47 (43%)	52 (45%)	1 (ref)
5–9	117 (52%)	57 (52%)	60 (52%)	0·86
≥10	9 (4%)	5 (5%)	4 (3%)	0·64
Median number of rooms	5 (2–9)	5 (1–9)	5 (2–9)	0·69
Number of rooms for sleeping				
1–2	127 (56%)	58 (53%)	69 (59%)	1 (ref)
2–4	93 (41%)	48 (44%)	45 (39%)	0·38
≥4	5 (2%)	3 (3%)	2 (2%)	0·53
Median number of rooms for sleeping	2 (1–4)	2 (1–4)	2 (1–4)	0·42
Crowding (>2 people per sleeping room)	110 (49%)	57 (52%)	53 (46%)	0·32
No crowding	115 (51%)	52 (48%)	63 (54%)	1 (ref)
Child aged <5 years in house	153 (68%)	96 (88%)	57 (49%)	<0·0001
No child aged <5 years in house	75 (32%)	13 (12%)	59 (51%)	1 (ref)
Household member smokes indoors	44 (20%)	9 (8%)	35 (30%)	<0·0001
No household member smokes indoors	181 (80%)	100 (92%)	81 (70%)	1 (ref)
Main water source tap inside	115 (51%)	57 (52%)	58 (50%)	0·73
Handwashing place with water in house	182 (81%)	69 (63%)	113 (97%)	<0·0001
No handwashing place with water in house	43 (19%)	40 (37%)	3 (3%)	1 (ref)
Main fuel for cooking				
Electricity	183 (81%)	74 (68%)	109 (94%)	<0·0001
Wood	36 (16%)	35 (32%)	1 (1%)	1 (ref)
Paraffin, gas, or other	5 (2%)	0	5 (4%)	NE
Monthly household income*				
≤R800 (≤$54)	28 (13%)/219	15 (14%)/105	13 (11%)/114	1 (ref)
R801–1600 ($55–108)	64 (29%)/219	30 (29%)/105	34 (30%)/114	0·56
R1601–3200 ($109–116)	71 (32%)/219	38 (36%)/105	33 (29%)/114	1·00
R3201–6400 ($117–232)	44 (20%)/219	17 (16%)/105	27 (24%)/114	0·22
R6401–12800 ($233–464)	8 (4%)/219	5 (5%)/105	3 (3%)/114	0·66
>R12800 (>$464)	4 (2%)/219	0	4 (4%)/114	NE
Summer indoor PM4 >25μg/m^{-3}†	89 (46%)/193	57 (61%)/94	32 (32%)/99	<0·0001
Summer indoor PM4 ≤25 μg/m^{-3}†	104 (54%)	37 (39%)	67 (68%)	1 (ref)
Winter indoor PM4 >25μg/m^{-3}†	152 (78%)/193	60 (63%)/94	92 (93%)/99	<0·0001
Winter indoor PM4 ≤25μg/m^{-3}†	44 (22%)	36 (38%)	8 (8%)	1 (ref)
Indoor summer temperature, °C‡	22 (19–25)	24 (21–25)	21 (19–23)	<0·0001
Indoor winter temperature, °C‡	16 (9–20)	18 (16–20)	12 (8–16)	<0·0001

Data are n (%), n (%)/N, or median (IQR) unless otherwise specified. p values compared characteristics of households between the urban and rural site using logistic regression adjusted for clustering by site and household. NE=not estimated. R=South African Rand. *Household income was rounded to the nearest R equivalent value in US$ reported. †Median respirable particulate matter over a 7-day sampling period. ‡Median indoor temperature over a 7-day sampling period in degrees centigrade; available for 196 households (96 in the rural setting and 100 in the urban setting).

Table 1: **Baseline characteristics of households in a rural and an urban setting in South Africa, 2017–18**

	Overall (n=1116)	Rural (n=561)	Urban (n=555)	p
Age group (years)				
<1	22 (2%)	9 (2%)	13 (2%)	0·028
1–4	158 (14%)	104 (19%)	54 (10%)	1 (ref)
5–12	302 (27%)	166 (30%)	136 (25%)	0·025
13–18	161 (14%)	84 (15%)	77 (14%)	0·014
19–44	291 (26%)	124 (22%)	167 (30%)	<0·0001
45–64	137 (12%)	52 (9%)	85 (15%)	<0·0001
≥65	45 (4%)	22 (4%)	23 (4%)	0·041
Sex				
Female	680 (61%)	358 (64%)	322 (58%)	<0·0002
Male	436 (39%)	203 (36%)	233 (42%)	1 (ref)
Year of active follow-up				
2018	558 (50%)	276 (49%)	282 (51%)	0·3009
2017	558 (5%)	285 (51%)	273 (49%)	1 (ref)
Level of education*				
No schooling	52 (11%)/485	42 (21%)/203	10 (4%)/282	1 (ref)
Primary schooling	111 (23%)/485	50 (25%)/203	61 (22%)/282	0·001
≥1 year of secondary schooling	183 (38%)/485	44 (22%)/203	139 (49%)/282	0·303
Secondary completed	123 (25%)/485	62 (31%)/203	61 (22%)/282	0·52
Post-secondary	16 (3%)/485	5 (2%)/203	11 (4%)/282	0·16
Employment status*				
Unemployed	272 (56%)/485	131 (65%)/203	141 (50%)/282	1 (ref)
Employed	183 (38%)/485	56 (28%)/203	127 (45%)/282	<0·0001
Student	30 (6%)/485	16 (8%)/203	15 (5%)/282	0·59
Reported alcohol use†	217 (36%)/579	37 (15%)/248	180 (54%)/331	<0·0001
No reported alcohol use	362 (63%)	211 (85%)	151 (46%)	1 (ref)
Reported current cigarette smoking†	91 (16%)/579	11 (4%)/248	80 (24%)/331	<0·0001
No reported current cigarette smoking	488 (84%)	237 (96%)	251 (76%)	1 (ref)
Reported current snuff smoking†	63 (11%)/ 579	3 (1%)/248	60 (18%)/331	<0·0001
No reported current snuff smoking	516 (89%)	245 (99%)	271 (82%)	1 (ref)
Reported current cigarette or snuff smoking†	157 (27%)/579	14 (6%)/248	143 (43%)/331	<0·0001
No reported current cigarette or snuff smoking	422 (73%)	234 (94%)	188 (57%)	1 (ref)
Smoking inside‡	56 (36%)/157	2 (14%)/14	54 (38%)/143	0·099
No smoking inside	101 (64%)	12 (86%)	89 (62%)	1 (ref)
Urine cotinine (all ages)§				
Negative	437 (41%)/1070	356 (65%)/544	81 (15%)/526	1 (ref)
Passive exposure	466 (44%)/1070	169 (31%)/544	297 (56%)/526	<0·0001
Active smoking	167 (16%)/1070	19 (3%)/544	148 (28%)/526	<0·0001
HIV status§¶				
Uninfected	908 (84%)/1075	485 (88%)/553	423 (81%)/522	1 (ref)
Infected	167 (16%)/1075	68 (12%)/553	99 (19%)/522	0·0025
ART use in those with HIV				
Currently receiving	142 (85%)/167	55 (81%)/68	87 (88%)/99	0·44
Not receiving	18 (11%)/167	9 (13%)/68	9 (9%)/99	1 (ref)
Not reported	7 (4%)/167	4 (6%)/68	3 (3%)/99	NE
HIV viral suppression in those receiving ART				
Suppressed throughout	53 (37%)/142	16 (29%)/55	37 (43%)/87	0·46
Became suppressed during study	27 (19%)/142	18 (33%)/55	9 (10%)/87	NE
Suppressed at some point	6 (4%)/142	3 (5%)/55	3 (3%)/87	0·56

(Table 2 continues on next page)

HIV-negative if they had a documented negative HIV result in the previous 6 months. Patients newly diagnosed with HIV were referred for assessment and initiation of antiretroviral therapy.

Episodes and clusters of influenza infection were estimated separately by virus subtype or lineage (appendix p 39). We considered an infection to be new when the individual tested positive for a different influenza subtype or lineage or the same subtype or lineage more than 2 weeks after the last day of previous positivity; all other instances were considered the same episode. These criteria were used because individuals could test negative and then positive again due to fluctuations in viral load or specimen quality. We defined an influenza infection episode as at least one real-time RT-PCR positive (cycle threshold [Ct] value <37) nasopharyngeal swab for influenza. Episode duration was estimated from the first to the last day of real-time RT-PCR positivity. An illness episode was defined as an episode with one or more symptoms reported from one visit before to one visit after the influenza infection episode. Symptoms included fever (self-reported or measured tympanic temperature ≥38°C), cough, difficulty breathing, sore throat, nasal congestion, chest pain, muscle aches, headache, vomiting, and diarrhoea. Influenza-like illness was defined as fever and cough within an influenza-confirmed episode. We defined the length of the influenza season in each site every year from the first to the last date of any influenza-positive samples in the study cohort. Lower Ct value on real-time RT-PCR was used as a proxy for higher viral load.

A cluster included all infections of the same influenza subtype or lineage in a single household that occurred within an interval between infections of two or fewer mean serial intervals (7 days), including single infections. 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 positivity of the last individual. The household cumulative infection risk (HCIR) was defined as the number of subsequent infections within a household cluster following influenza introduction. The index case was defined as the first individual testing positive within a cluster. Households with coprimary cases were excluded from the HCIR analysis.

Outcomes

The primary objectives were to estimate the community burden of influenza including the incidence, symptomatic fraction, and fraction seeking medical care, and to assess the transmission dynamics, including estimation of the HCIR, serial interval, and length of shedding. Secondary objectives included estimation of the community burden and transmission dynamics by age group, HIV status, and other factors, and the assessment of the role of asymptomatic individuals in household transmission of influenza.

Statistical analysis

We aimed to enrol approximately 1500 individuals over three consecutive seasons (Jan 15–Oct 31, 2016–18). To allow the annual estimation of up to 30% risk of infection and a 10–20% risk of illness—with 95% CI and 5% desired precision and assuming design effect of 1·5—we aimed to include at least 484 individuals each year. Assuming an average household size of five individuals and loss to follow-up of approximately 10%, we targeted enrolling 110 households each year. Reliable symptom data were only available for the 2017 and 2018 influenza seasons, and data from these years were included in the analysis. Data from 2016 were not included because our analyses focus on the contribution of asymptomatic individuals to influenza burden and transmission and the data from the first year of the study did not include this information.

Proportions of individuals seeking medical care and those who were absent from work were compared using the χ^2 test. We defined incidence of influenza infection or illness episodes as the number of episodes divided by the person time under observation, reported per 100 person-seasons. Serial interval was calculated as the date difference between PCR-positive index case and the subsequent secondary case. A mean serial interval was then calculated. All secondary cases with PCR positivity less than 12 days after the index case were included in analyses of serial interval and HCIR. With these definitions, it was possible for a household to experience more than one cluster of infection by the same subtype or lineage or a different subtype or lineage in the same season.

For the analysis of factors associated with time-to-event outcomes (duration of shedding and serial interval) we used accelerated time failure Weibull regression. Logistic regression was used for the analysis of factors associated with binary outcomes (symptomatic fraction and HCIR). Factors associated with incidence were assessed with Poisson regression to account for multiple infections during the same influenza season in some individuals. For analysis of incidence, we considered all identified episodes of infections, including instances of more than one infection episode in the same individual within the same season. In addition, we did an analysis considering at least one episode per season (excluding multiple infections). For all analyses we accounted for within-household clustering using the Taylor-linearised variance estimation (svy Stata function). For each multivariable model we considered all a priori probably biologically associated factors with the outcome of interest for which we had available data. Age was included in all models as an important possible confounder. We examined factors associated with different outcomes; therefore, the selected predictors varied across models. Once we had developed the final models, we implemented a final model check using forward and backward selection.

	Overall (n=1116)	Rural (n=561)	Urban (n=555)	p
(Continued from previous page)				
Never suppressed	40 (28%)/142	15 (27%)/55	25 (29%)/87	1 (ref)
No viral load results	16 (11%)/142	3 (5%)/55	13 (15%)/87	0·18
Previous tuberculosis	57 (5%)	11 (2%)	46 (8%)	<0·0001
No previous tuberculosis	1059 (95%)	550 (98%)	509 (92%)	1 (ref)
Current tuberculosis	18 (2%)	1 (<1%)	17 (3%)	0·005
No current tuberculosis	1098 (98%)	560 (>99%)	538 (97%)	1 (ref)
Other underlying illness‖	27 (2%)	1 (<1%)	26 (5%)	<0·0001
No other underlying illness	1089 (98%)	560 (>99%)	529 (95%)	1 (ref)
Influenza vaccination	1 (<1%)	0	1 (<1%)	NE
No influenza vaccination	1115 (>99%)	561 (100%)	554 (>99%)	1 (ref)
Pneumococcal vaccine up to date for age**				
Yes	150 (96%)/156	95 (98%)/97	55 (93%)/59	1 (ref)
No	6 (4%)/156	2 (2%)/97	4 (7%)/59	0·16
DTaP-IPV/Hib vaccine up to date for age‖**				
Yes	152 (97%)/157	95 (98%)/97	57 (95%)/60	1 (ref)
No	5 (3%)/157	2 (2%)/97	3 (5%)/60	0·32

Data are n (%) or n (%)/N. p value compared characteristics of individuals between the urban and rural site using logistic regression adjusted for clustering by site and household. ART=antiretroviral therapy. DTaP-IPV/Hib=Diphtheria, tetanus, acellular pertussis, inactivated polio, *Haemophilus influenzae* type B vaccine. NE=not estimated. *Individuals who were 18 years or older were included. †Individuals who were 15 years or older were included. ‡Of those who reported any current smoking. §Percentage and p value in individuals with known urine cotinine status; all individuals were eligible for urine cotinine testing. ¶Of the 167 people with HIV, 141 with available CD4 T-cell count data, 102 (72%) had CD4 T-cell counts more than 500 cells per µl (36 at rural site, 66 at urban site), 31 (22%) had 200–500 cells per µl (22 at rural site, 9 at urban site), and 8 (6%) had less than 200 per µl (4 at each site). ‖Self-reported history of asthma, lung disease, heart disease, stroke, spinal cord injury, epilepsy, organ transplant, immunosuppressive therapy, organ transplantation, cancer, liver disease, renal disease, or diabetes. **Individuals younger than 5 years with available data are reported.

Table 2: **Baseline characteristics of individuals included in PHIRST at a rural and an urban site, South Africa, 2017–18**

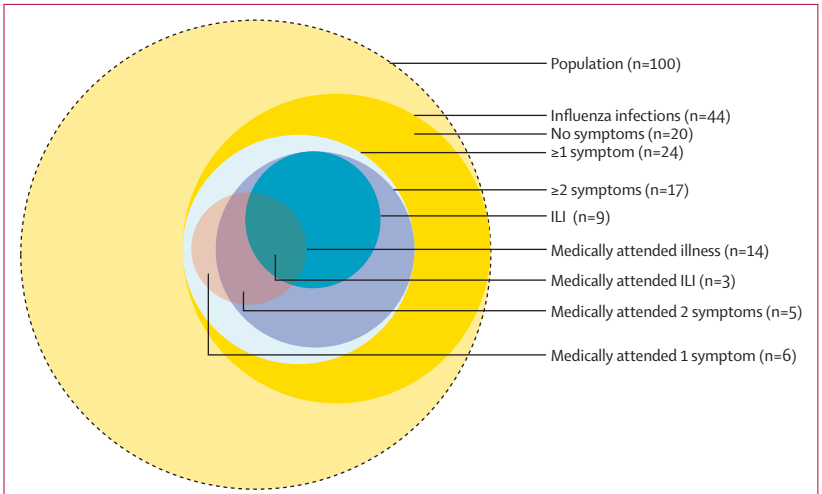

Figure 1: **Estimated number of influenza infection episodes by symptoms and medical attendance per season in a population of 100 individuals**
ILI=influenza-like illness

Pairwise interactions were assessed graphically and by inclusion of product terms for all variables in the final multivariable additive model. We did all statistical analyses using STATA (version 14.1). For each univariate

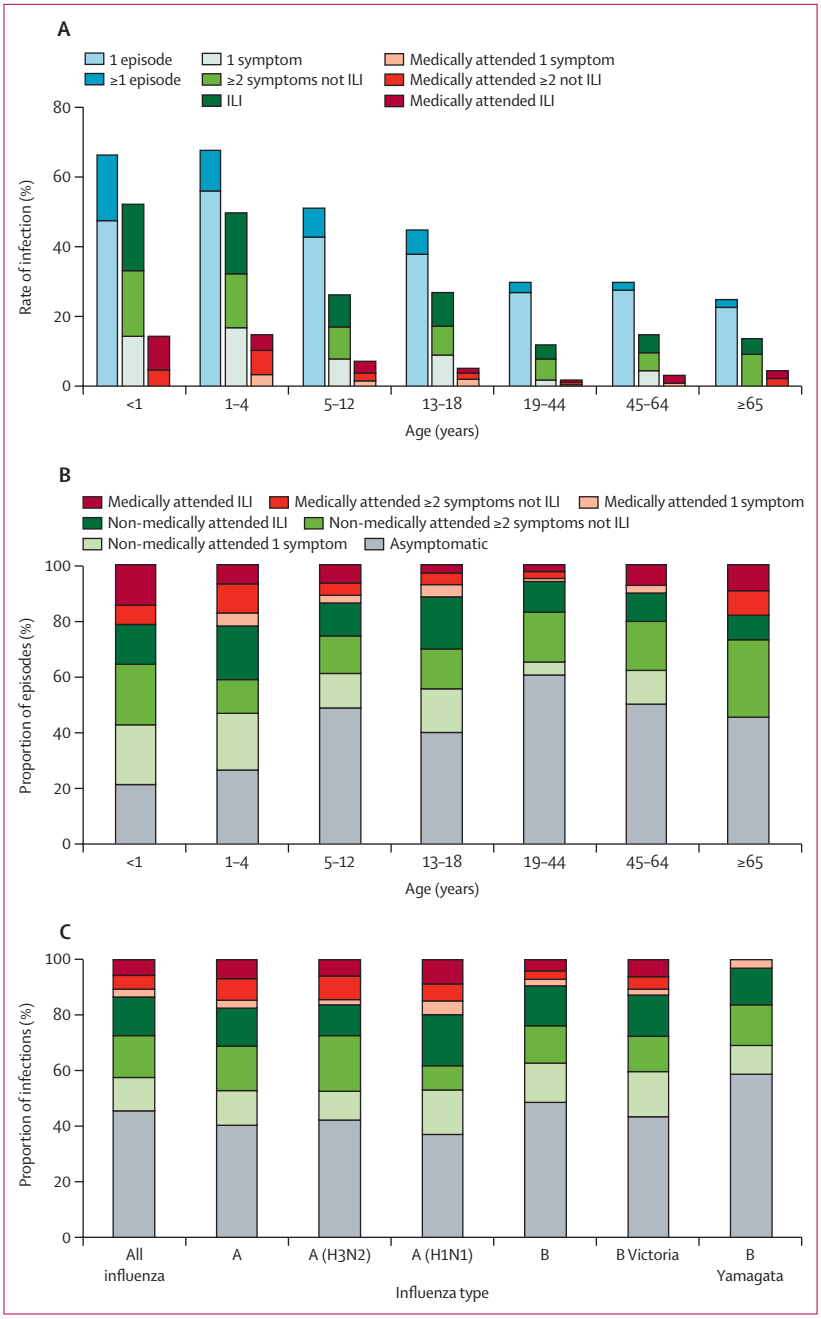

Figure 2: **Rates of influenza infections and influenza-associated illness per 100 person-seasons by age group (A), and the proportion of episodes by symptom and medical attendance by age group (B), and influenza type, subtype and lineage (C)**
ILI=influenza like illness.

analysis, we used all available case information. Sensitivity analyses are described in the appendix (pp 6–7). This study is registered on ClinicalTrials.gov, NCT02519803.

Role of the funding source

The study sponsor had no role in the design, data collection, or implementation of the study, or the analysis or reporting of the results.

Results

From Nov 24, 2016, to Feb 24, 2017, (2017 cohort) and Nov 28, 2017, to Feb 24, 2018, (2018 cohort) we approached 670 households, of which 287 (42%) agreed to participate in the study. 225 (78%) households were included in the analysis. Of the 1176 individuals approached, 1116 (95%) were included in the analysis (appendix p 40).The median number of household members was five (IQR 3–10), with a median of two rooms (IQR 1–4) for sleeping. 153 (68%) of 225 households had a child younger than 5 years, with a higher proportion in the rural setting ($p<0·0001$; table 1). A higher proportion of individuals in the rural setting were younger than 18 years, had a lower level of education, were more likely to be unemployed, and less likely to be exposed to cigarette smoke (table 2). Current and previous tuberculosis and other underlying illnesses were more common in the urban site, but HIV prevalence was similar between sites (table 2).

Nasopharyngeal swabs were collected and tested at 81430 (90·4%) of 90041 potential follow-up visits, of which 917 (1%) tested positive for influenza on real-time RT-PCR (appendix pp 42–47). 178 (79%) of 225 households had at least one individual who tested positive for influenza, with a mean of 1·7 (SD 1·3) clusters and 2·3 (1·3) infected individuals per infected household (appendix p 18). The incidence of influenza infection was 43·6 (95% CI 39·8–47·7) per 100 person-seasons and the incidence of illness (individuals with at least one symptom) was 24·4 per 100 person-seasons; incidence of influenza-like illness (fever and cough) was 8·6 per 100 person-seasons (figure 1; appendix p 20). Incidence was highest in children younger than 5 years and decreased with increasing age (67·4 per 100 person-season in children <5 years; $p<0·0001$; figure 2A; appendix p 20). 268 (56%) of 478 infections were associated with one or more symptoms, and 94 (20%) were associated with influenza-like illness (fever and cough), with a higher proportion of symptomatic infections in children younger than 5 years (figure 2B; appendix p 19). The most common symptoms reported in 268 individuals with symptoms were cough (206 [77%] participants), runny nose (188 [70%]), and fever (103 [38%]). 66 (14%) of 478 infections were medically attended; the rate of medically attended influenza-associated illness was 6·0 per 100 person-seasons and was proportionally highest in the extremes of age (appendix p 20). 66 (25%) of 268 individuals with symptoms sought medical care. 95 (57%) of the 168 individuals with symptoms who attended school or work reported absenteeism (appendix p 23). Absenteeism was more common in individuals with two or more symptoms (appendix p 23).

Of the 408 individuals who had at least one influenza infection, 66 (16%) had a second influenza infection and 3 (1%) had three influenza infections within the same season. 22 (23%) of 97 children younger than 5 years had a repeat infection. Repeat infections were most

	Symptomatic illness	Univariate OR† (95% CI)	Multivariable adjusted OR† (95% CI)
Age (years)			
<1	11/14 (79%)	6·4 (1·4–29·0)	2·2 (0·4–11·4)
1–4	77/106 (73%)	4·8 (2·4–9·8)	2·3 (1·1–5·0)
5–12	79/154 (51%)	1·7 (0·9–3·1)	1·1 (0·6–2·2)
13–18	42/71 (59%)	2·4 (1·2–5·0)	1·9 (0·8–4·3)
19–44	33/84 (39%)	1 (ref)	1 (ref)
45–64	20/40 (50%)	1·5 (0·6–3·6)	1·8 (0·7–4·5)
≥65	6/11 (55%)	1·9 (0·4–8·0)	2·4 (0·5–10·9)
p†		<0·0001	0·20
Gender			
Female	155/286 (54%)	0·9 (0·6–1·3)	..
Male	113/194 (58%)	1 (ref)	..
p†		0·45	..
HIV status			
Infected	28/59 (47%)	0·7 (0·4–1·2)	..
Uninfected	228/401 (57%)	1 (ref)	..
p†	..	0·18	..
Other underlying illness			
Absent	261/469 (56%)	1 (ref)	..
Present	7/11 (64%)	1·4 (0·3–5·8)	..
p†		0·64	..
Body-mass index			
Underweight	27/46 (59%)	1·1 (0·5–2·2)	..
Normal weight	181/313 (58%)	1 (ref)	..
Overweight	25/61 (41%)	0·4 (0·2–0·8)	..
Obese	35/60 (58%)	1·0 (0·5–1·9)	..
p†	..	0·10	..
Duration of shedding (days)			
≤3	87/225 (39%)	1 (ref)	1 (ref)
4–7	75/117 (64%)	4·1 (2·2–7·4)	2·5 (1·3–4·6)
8–12	61/78 (78%)	7·4 (3·6–15·1)	4·2 (1·9–8·9)
≥13	45/60 (75%)	6·8 (3·1–15·2)	3·9 (1·7–9·3)
p†	..	<0·0001	<0·0001
(Table 3 continues in next column)			

	Symptomatic illness	Univariate OR† (95% CI)	Multivariable adjusted OR† (95% CI)
(Continued from previous column)			
Minimum Ct value			
<30	222/476 (66%)	4·2 (2·6–6·8)	2·5 (1·5–4·4)
≥30	46/138 (33%)	1 (ref)	1 (ref)
p†	..	<0·0001	<0·0001
Subtype or lineage			
Influenza A (H3N2)	98/167 (59%)	2·0 (1·1–3·7)	2·4 (1·2–4·9)
Influenza A (H1N1) pdm09	56/89 (63%)	2·6 (1·2–5·4)	3·3 (1·4–7·8)
Influenza B Victoria	83/147 (56%)	1·8 (0·9–3·5)	2·2 (1·0–4·6)
Influenza B Yamagata	31/73 (42%)	1 (ref)	1 (ref)
Influenza A (H3N2) or Influenza B Yamagata, or both	0/2	Not estimated	Not estimated
p†	..	0·072	0·038
Winter indoor PM4‡			
≤25 μg/m^{-3}	61/93 (66%)	1 (ref)	..
>25 μg/m^{-3}	184/344 (53%)	0·6 (0·3–1·0)	..
p†	..	0·066	..

Data are n/N (%) unless otherwise stated. Additional factors evaluated but not found to be statistically significant include year, site, employment, education level, alcohol, smoking, cotinine level, underlying tuberculosis, receipt of influenza vaccine. The analysis was repeated excluding two individuals with mixed infection and results remained unchanged for all other covariates. OR=odds ratio. Ct=cycle threshold. *One or more symptoms *vs* no symptom reported. †Estimated using logistic regression adjusted for clustering by site and household. ‡PM4 mean respirable particulate matter over 7-day sampling period.

Table 3: **Factors associated with symptomatic illness* in individuals with influenza at a rural or an urban site in South Africa, 2017–18**

commonly (59 [82%] of 72 infections) with a different virus type, subtype, or lineage (appendix p 24) and were more common in children younger than 18 years (appendix p 20). 326 (73%) of 447 influenza episodes for which the index case could be determined were presumed acquired in the community (ie, the individuals were the index case in their household).

Annual rates of influenza infection varied by type and subtype, but the overall rates per 100 person-seasons were similar for influenza A (23·5 [95% CI 20·8–26·6) and influenza B (20·2 [17·7–23·1]; appendix p 24). Rates of medically attended illness were higher for influenza A (4·0 [95% CI 3·0–5·4) compared with influenza B (1·8 [1·2–2·8]; appendix p 25) per 100 person-season. Variation by subtype and lineage are reported in figure 2C and the appendix (pp 25–27, 48).

On multivariable analysis, factors associated with symptomatic compared with asymptomatic infection were age group 1–4 years versus 19–44 years, shedding duration of more than 3 days, real-time RT-PCR Ct value less than 30, and influenza A (H3N2), influenza A (H1N1) pdm09, or influenza B Victoria versus influenza B Yamagata (table 3).

The median duration of shedding was 6·5 days (SD 4·8; IQR 3–10). On multivariable analysis, factors associated with longer episode duration were age (<18 years *vs* 19–44 years), presence of symptoms, and real-time RT-PCR Ct less than 30 (adjusted hazard ratio 0·3 [95% CI 0·2–0·4]; appendix pp 28–29).

The mean interval between first positive PCR in the index case and secondary case was 5·9 days (SD 2·6; figure 3). Multivariable analysis suggests that factors associated with a serial interval were index and contact age and two or more symptoms in index case (appendix pp 30–31). Sensitivity analysis restricted to individuals with serial interval of less than 8 days showed that the factors associated with serial interval were similar to those identified in individuals with a serial interval of less than 12 days (appendix pp 32–33).

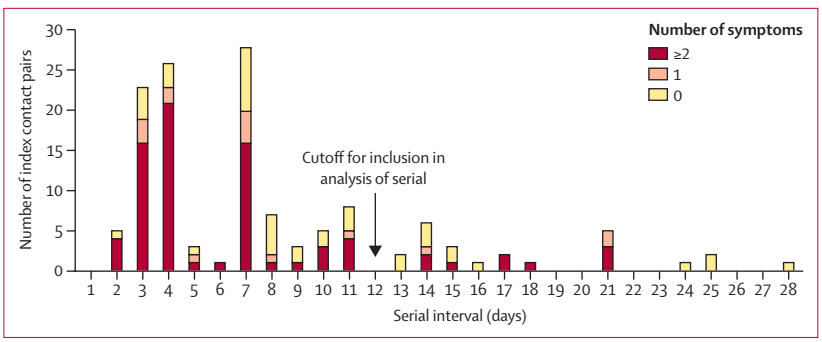

Figure 3: **Interval between first influenza-positive real-time RT-PCR in the index case and first positive real-time RT-PCR in household contacts (serial interval)**
133 participants. 68 (51%) from the rural and 65 (49%) from the urban setting were included.

The overall HCIR was 10% (109 of 1088 exposed household members infected [95% CI 9–13%). Transmission was highest from index cases with two or more symptoms (68 [17%] of 396 cases [95% CI 14–21%]) and children aged 1–4 years (40 [16%] of 252 children). 29 (6%) of 509 (95% CI 4–8) of the household contacts of asymptomatic individuals infected with influenza acquired influenza infection from the asymptomatically infected individual (table 4). About a quarter (29 [27%] of 109) of all secondary influenza infections were acquired from asymptomatic index cases. On multivariable analysis, factors associated with increased transmission were age of the index case (1–4 years *vs* 13–18 years), number of symptoms (≥2 symptoms *vs* no symptoms), and a duration of shedding of more than 3 days. Being younger than 12 years or in the 19–44-year age group compared with the 13–18-year age group were associated with increased odds of influenza acquisition. On sensitivity analysis, including all subsequent cases within the household or restricting to secondary cases less than 8 days after index onset, results remained similar (appendix pp 34–37).

Discussion

In two communities in South Africa, the annual incidence of influenza infection was high and repeat infection within the same year was common. Rates of influenza infection and repeat infections were highest in children younger than 5 years and decreased with increasing age. Young children were more likely to transmit influenza. Approximately half of all infections were symptomatic and 14% were medically attended. Medically attended illness was more common in the extremes of age (individuals ≤18 years or ≥65 years). Asymptomatic individuals transmitted influenza, but at approximately half the rate of individuals with two or more symptoms. HIV infection was not associated with influenza burden or transmission. Findings were generally consistent in the rural and urban setting.

We describe a high rate of PCR-confirmed influenza infection of more than 40 per 100 person-seasons, with an individual with influenza reported in more than 75% of households; more than 35% of individuals had at least one infection annually, and 17% of individuals had a repeat infection in the same year. There are no similar studies of influenza community infection incidence measured by frequent sampling and testing for influenza with PCR irrespective of symptoms. The most similar data are probably those from cohort studies that collected sera before and after the influenza season, with infection defined as a four-times or higher increase in antibody titres.[4] However, some individuals with detectable shedding do not seroconvert and some individuals with seroconversion do not have evidence of shedding.[12,17,18–21] Several studies, including data from the USA, the UK, Vietnam, and New Zealand, have identified annual community rates of influenza infection ranging from 15–35%.[4,5,22] The Fluwatch study[4] from the UK found rates of infection of 18%, but children younger than 5 years were excluded. The SHIVERS study[5] from New Zealand, which evaluated seroconversion using criteria for both haemagglutinin and neuraminidase inhibition found similar results to our study with an overall infection rate of 32% and rates of more than 40% in children younger than 19 years. A cohort study from Vietnam found slightly lower overall rates of infection (17–26%), possibly because they only assessed haemagglutinin inhibition and not neuraminidase inhibition.[22] Similar to our study, the cohort study from Vietnam also reported that approximately 10% of individuals had repeat infections with different virus types and subtypes (including some with three different infections) within the same season. In our study, it is possible that some of the identified repeat infections represent prolonged intermittent shedding, but more than 80% of infections were with a different influenza type or subtype.

Systematic reviews of the proportion of symptomatic influenza infections have identified heterogeneity in estimates.[17,23] We found that just over half of all PCR-confirmed infections were symptomatic, falling between estimates from studies of outbreak investigations (4–28%) and those from serological studies (65–85%).[17] Heterogeneity in estimates of symptomatic fraction could be because of biological factors (eg, infections acquired in the community are milder on average than those in household outbreaks because of less intense exposure) or differences in illness reporting or criteria for seroconversion. PHIRST has the advantage of assessing both community-acquired and household-acquired infections systematically, and the study might represent a more robust estimate. Variation in the proportion of individuals with influenza who have one or more symptoms by age is plausible because both illness severity and immunity change substantially with age, although data are few in number.[17] We found that the proportion of individuals with symptomatic infection was reduced with increasing age, but that medically attended illness was proportionately highest at the extremes of age (≤18 years or ≥65 years).

	HCIR	Univariate OR (95% CI)†	Multivariable adjusted OR (95% CI)†
Characteristics of the index case			
Age group (years)			
<1	2/13 (15%; 2–45)	2·5 (0·3–20·2)	2·2 (0·2–20·0)
1–4	40/252 (16%; 12–21)	3·9 (1·6–9·6)	3·1 (1·2–8·2)
5–12	37/352 (11%; 8–14)	2·3 (0·9–5·6)	2·5 (1·0–6·3)
13–18	14/213 (7%; 4–11)	1 (ref)	1 (ref)
19–44	10/154 (6%; 3–12)	1·4 (0·5–4·2)	2·5 (0·8–8·0)
45–64	4/80 (5%; 1–12)	0·7 (0·2–2·9)	1·0 (0·2–4·2)
≥65	2/24 (8%; 1–27)	1·4 (0·2–11·3)	2·1 (0·2–20·0)
p†	..	0·039	0·30
Gender			
Female	69/669 (10%; 8–13)	1·4 (0·8–2·4)	..
Male	40/419 (10%; 7–13)	1 (ref)	..
p†	..	0·24	..
HIV status			
Infected	8/98 (8%; 4–15)	0·9 (0·4–2·4)	..
Uninfected	100/959 (10%; 9–13)	1 (ref)	..
p†	..	0·88	..
Number of symptoms			
None	29/509 (6%; 4–8)	1 (ref)	1 (ref)
1	12/183 (7%; 3–11)	1·0 (0·4–2·2)	0·5 (0·2–1·3)
≥2	68/396 (17%; 14–21)	3·6 (2·0–6·5)	2·1 (1·1–4·2)
p†	..	<0·0001	0·0018
Duration of shedding (days)			
<4	18/558 (3%; 2–5)	1 (ref)	1 (ref)
4–10	55/355 (15%; 12–20)	6·5 (3·4–12·7)	7·9 (3·6–17·2)
>10	35/164 (21%; 15–28)	7·3 (3·5–15·3)	7·6 (3·1–18·3)
p†	..	<0·0001	<0·0001
Subtype or lineage			
Influenza A (H3N2)	46/463 (10%; 7–13)	1·3 (0·7–2·6)	..
Influenza A (H1N1) pdm09	21/227 (9%; 6–14)	1·0 (0·4–2·4)	..
Influenza B Victoria	43/292 (15%; 11–19)	2·0 (0·9–4·5)	..
Influenza B Yamagata	17/200 (9%; 5–13)	1 (ref)	..
p†	..	0·12	..
Minimum Ct value			
<30	95/683 (14%; 11–17)	7·1 (3·4–14·9)	..
≥30	13/394 (3%; 2–6)	1 (ref)	..
p†	..	<0·0001	..
(Continued from previous column)			
Characteristics of the household contact			
Age (years)			
<1	7/20 (35%; 15–59)	13·6 (3·4–54·0)	41·9 (8·4–207·5)
1–4	26/163 (16%; 11–22)	3·5 (1·5–8·4)	8·7 (3·0–24·5)
5–12	38/318 (12%; 9–16)	2·1 (1·0–4·8)	3·5 (1·3–9·1)
13–18	11/164 (7%; 3–12)	1 (ref)	1 (ref)
19–44	34/313 (11%; 8–15)	1·8 (0·8–3·9)	2·8 (1·1–7·2)
45–64	10/160 (6%; 3–11)	1·0 (0·4–2·6)	1·5 (0·5–4·6)
≥65	1/44 (2%; 0–12)	0·3 (0·0–3·2)	0·7 (0·1–7·7)
p†	..	<0·0001	<0·0001
Gender			
Female	82/715 (11%; 9–14)	1·2 (0·8–1·8)	..
Male	45/467 (10%; 7–13)	1 (ref)	..
p†	..	0·45	..
HIV status			
Infected	22/178 (12%; 8–18)	1·1 (0·6–2·0)	..
Uninfected	102/966 (11%; 9–13)	1 (ref)	..
p†	..	0·66	..
Other underlying illness			
Absent	122/1159 (11%; 9–12)	1 (ref)	..
Present	5/23 (22%; 7–44)	1·5 (0·4–5·4)	..
p†	..	0·52	..

Data are n/N (%; 95% CI), unless otherwise stated. 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 concentration of index or contact, underlying tuberculosis, other underlying illness of index, body-mass index of index case 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. Ct=cycle threshold. HCIR=household cumulative infection risk. OR=odds ratio. *Number of infections following pathogen introduction into a household, restricted to secondary cases with first influenza-positive <12 days after the index case first positive. †Estimated using logistic regression adjusted for clustering by site and household.

Table 4: **Factors associated with HCIR* at a rural and an urban site in South Africa, 2017–18**

A review published in 2014, showed that 36–71% of symptomatic influenza episodes have reported fever, and 15–40% of people with PCR-confirmed influenza seek medical care, with higher care seeking by the parents or carers of children younger than 5 years with influenza.[4] We found that 36% of patients with symptomatic episodes reported fever and cough, and care is sought by 25% of individuals with illness episodes or when experiencing illness episodes, with individuals in extremes of age (≤18 years or ≥65 years) most commonly seeking. Our estimated rates of influenza-associated illness (24·4 per 100 person-seasons) are similar to those from the UK Fluwatch (23 per 100 person-seasons),[4] but higher than those from a review of incidence of symptomatic influenza in the USA (3–11%).[21] Our influenza-like illness rates of 8·6 per 100 person-seasons are similar to estimates from Peru (10 per 100 person-years).[24]

A systematic review of influenza household transmission studies, found that the secondary infection risk for PCR-confirmed influenza in household contacts ranged from 1% to 38%,[10] with similar estimates in

subsequent publications.[25–27] The systematic review[10] identified an important outstanding question: can asymptomatic individuals transmit influenza? In a case-ascertained study from South Africa, the HCIR was 25% (95% CI 20–30),[12] slightly higher than the 17% (14–21) observed in household contacts of patients with two or more symptoms in this study. In PHIRST, the overall HCIR was 11% (95% CI 9–13%), probably because of the inclusion of individuals who were asymptomatic and those with mild symptoms, in whom HCIR was 6% (4–8). Similar to previous studies, we could not be certain that all subsequent cases within a household were infected by the index case. A quarter of all secondary influenza infections in our study were from asymptomatic index cases, highlighting the importance of asymptomatic infections as drivers of influenza transmission.

The mean serial interval in our study was higher than the range of reported estimates of 2–4 days.[10] Serial intervals might vary in different settings because they depend on the infectivity profile of the index case, and it might be longer in studies, such as ours, in which index cases are identified in the community, and probably include a milder spectrum of illness. Serial intervals are also affected by contact patterns, transmission dynamics, and incubation periods. We found the serial interval was shorter in index cases with two or more symptoms confirming the importance of illness severity. Of note, because of the high proportion of asymptomatic infections in our study we defined serial interval as the interval between first positive PCR in the index case and first positive PCR on subsequent cases, to allow us to evaluate the effect of symptoms on serial interval. The median duration of shedding in our study was similar to a previous study from South Africa.[28] Similar to previous studies, we found that younger age, increasing number of symptoms, and higher viral load were associated with longer shedding duration.[29,30]

Young age was strongly associated with increased burden and transmission of influenza. Rates of influenza infection and symptomatic illness were highest in children younger than 5 years and decreased with increasing age. Children aged 1–4 years were more likely to transmit influenza to their household contacts. More symptoms and longer shedding duration were also associated with increased transmission; both these factors and young age were strongly associated with influenza viral load (indicated by low Ct values). Children aged 1–4 years were also more likely to be symptomatic. All of these suggest that biological factors—such as high viral load leading to longer duration of shedding and increasing symptom numbers—are important drivers of influenza burden and transmission. Age-specific contact patterns are also probably important contributors to transmission patterns. We did a nested study in this cohort for contact patterns in 2018 (appendix pp 4–5), and, when available, data from this study might be useful to understand the contribution of age-specific contact patterns.

The difficulty of ascertaining mild symptoms on repeated household visits has been reported since the early studies of household influenza transmission.[31] Some individuals might not have reported very mild symptoms. We attempted to minimise non-reporting by systematically asking participants about the presence or absence of ten symptoms at each visit, doing monthly field worker training on symptom data collection, and reiterating to participants the importance of reporting all symptoms at each visit. The public health relevance of individuals with mild symptoms who might have still been missed is unclear because they would have been unlikely to comply with recommendations targeting symptomatic individuals.

Our study had several limitations. It is possible that symptoms reported at the time of influenza infection were attributable to concurrent bacterial or viral infection and not influenza. It is possible that frequent household visits might have affected health-care seeking. Sampling for influenza every 3–4 days might have missed some infections of very short duration and we had missing influenza PCR data for 10% of follow-up visits. In some years, influenza circulation was ongoing at the end of the follow-up period. Together, these suggest that our estimates of influenza burden are a minimum estimate. Less than half of approached households agreed to participate in our study which could have introduced bias if included households differed from non-included households (appendix p 2). The rural and urban settings used in the study are approximately 600 km apart, and this might not be representative of other settings; however, the similar burden at both sites over 2 years—despite different climate and population characteristics—suggests that this finding might be representative, at least for South Africa. Numbers for some subgroup analyses were small, leading to wide CIs. Underlying illness was assessed by patient response, leading to possible under-reporting.

When compared with previous studies, our study had several strengths including high follow-up rates and frequent sampling by PCR, irrespective of symptoms, with systematic symptom ascertainment allowing for estimation of asymptomatic fraction and the role of asymptomatic infections in transmission.

In conclusion, we have shown a high burden of infection and illness in two South African communities over two influenza seasons, assessed to be of moderate severity through routine surveillance.[32] The burden is highest in young children and this group are important drivers of disease transmission. HIV is not associated with transmission. Asymptomatic infections make up almost half of all documented infections and individuals with asymptomatic infections transmitted influenza to 6% of household contacts suggesting that this group might be important drivers of transmission. These data have important implications for the implementation of measures to control influenza, such as early treatment,

quarantine, and isolation.[33,34] They will also inform the use of vaccination strategies focusing on reducing community influenza transmission.[3]

Contributors

CC, JM, MLM, FKT, OH, AvG, NW, and ST conceived of and designed the study. CC, JK, JM, MLM, FKT, OH, AzM, AvG, NW, NAM, KK, LL, KM, FW, FXG-O, TM, AnM, SP, BL, and ST collected data and did the laboratory processing. CC, JK, and ST accessed and verified the underlying data. CC and ST drafted the Article. All authors critically reviewed the Article. All authors had access to all the data reported in the study.

Declaration of interests

CC reports grants from Sanofi Pasteur, Advanced Vaccine Initiative, US Centers for Disease Control and Prevention, and the Billl & Melinda Gates Foundation; and travel fees from Parexel. AvG and NW report grants from Sanofi Pasteur and the Billl & Melinda Gates Foundation. NAM reports grants from Pfizer.

Data sharing

The study protocol, including informed consent forms, is available online. Analysis of the data for primary study objectives is planned to be completed by December, 2023. Additional modelling and serological studies will be concluded within one additional year and primary deidentified data will be made publicly available no later than December, 2025. The investigators welcome enquiries about possible collaborations and requests for access to the dataset. Data will be shared after approval of a proposal and with a signed data access agreement. Investigators interested in more details about this study, or in accessing these resources, should contact the corresponding author.

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