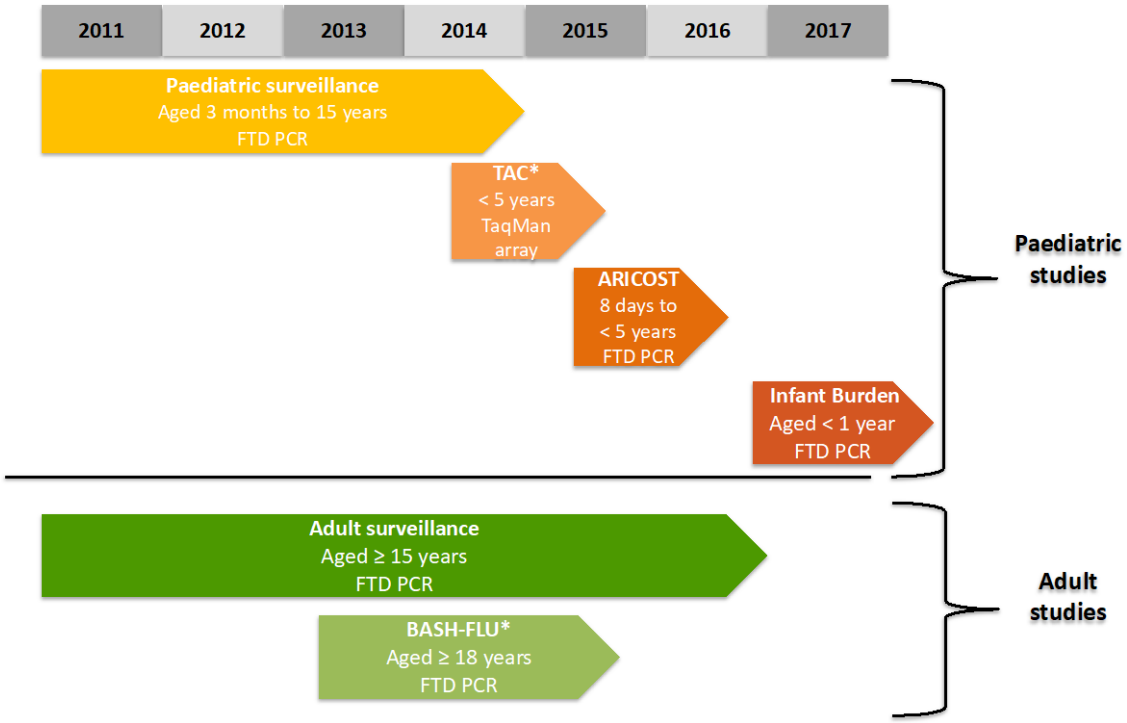
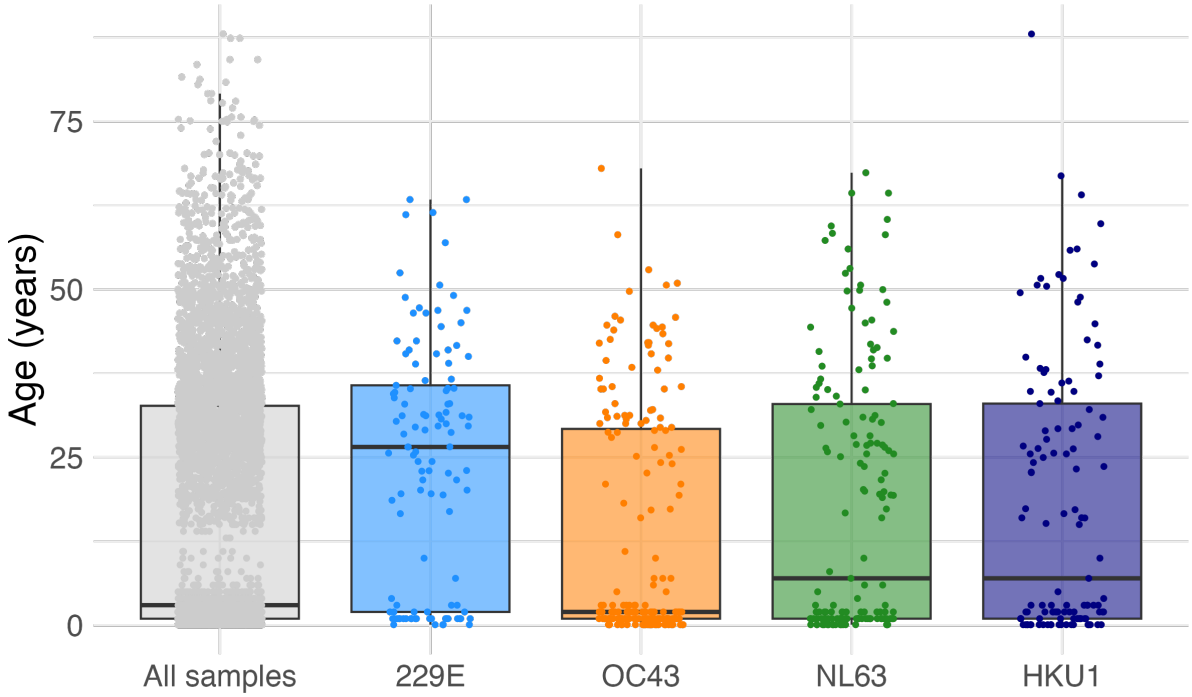
Supplementary material

Supplementary Figures



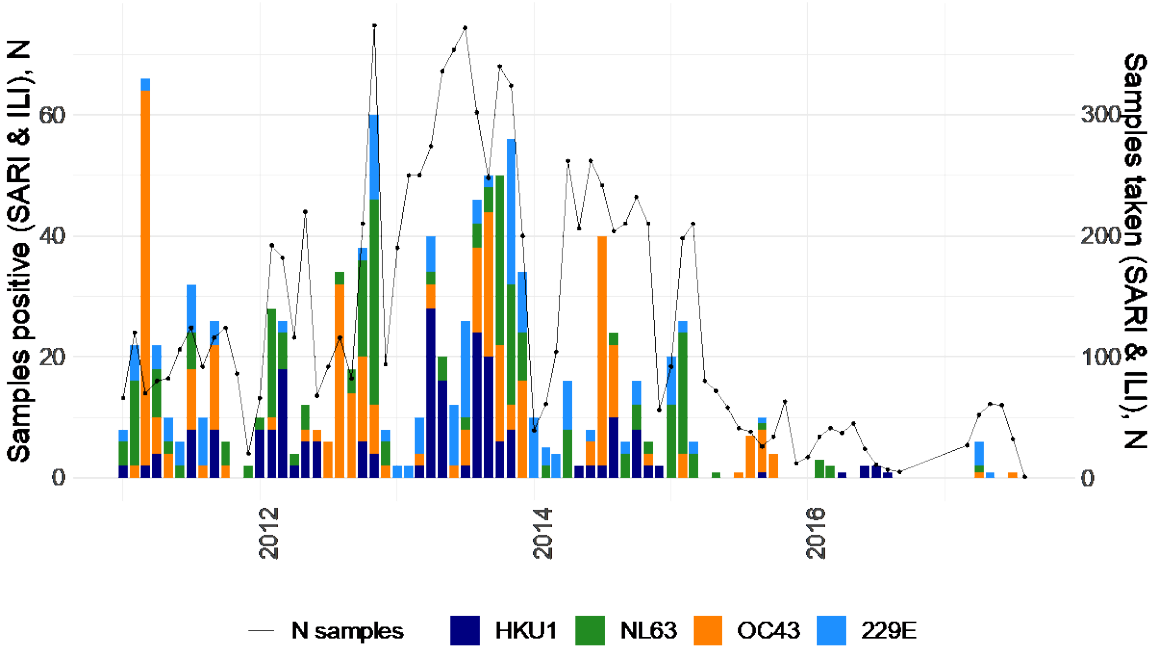
Supplementary Figure 1. Timeline, age categories and type of HCoV testing of included paediatric and adult studies and surveillance data

* Denotes studies that recruited asymptomatic controls.



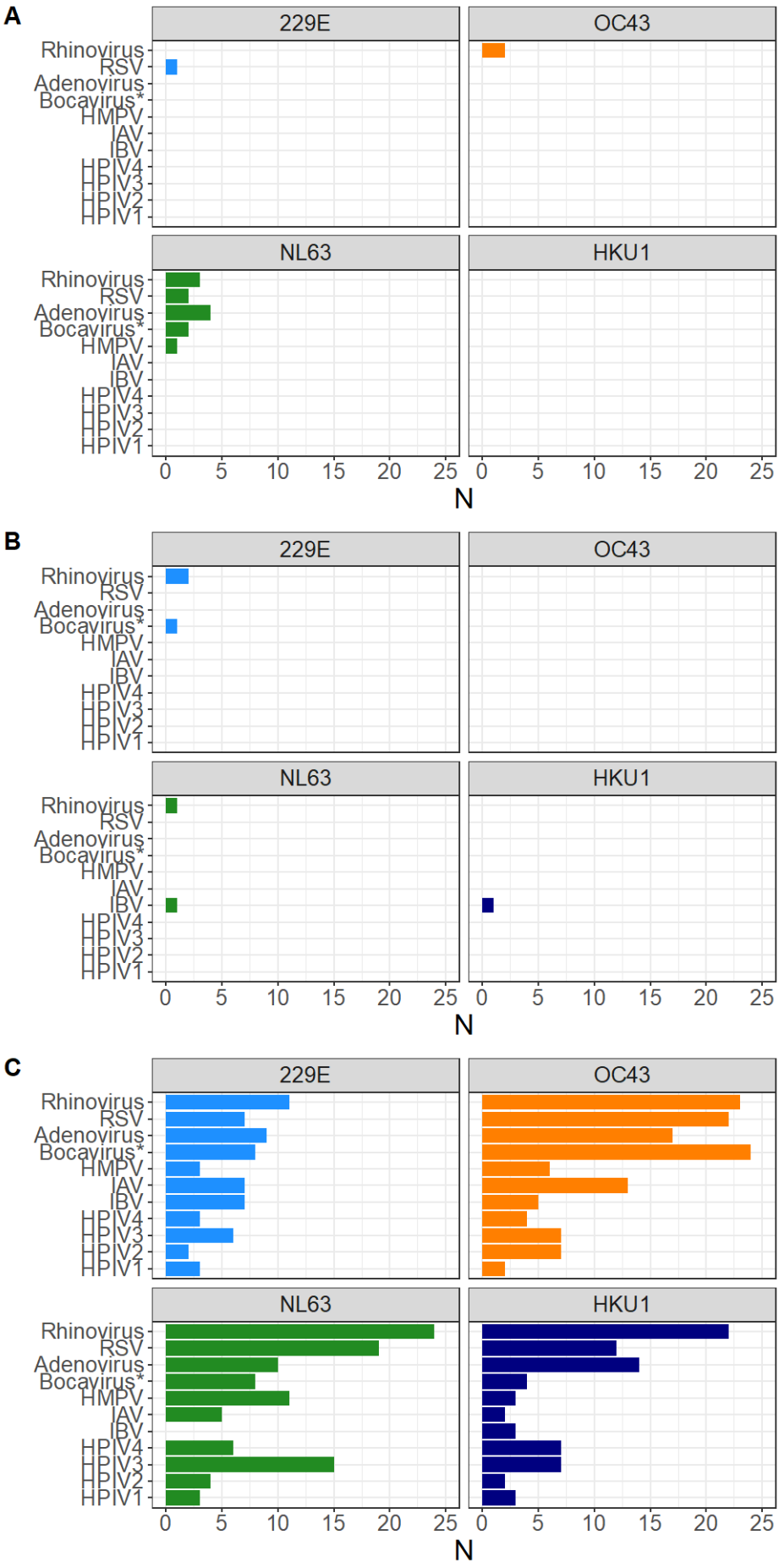
Supplementary Figure 2. Age distribution of all specimens taken and specimens positive for individual seasonal coronaviruses, Blantyre, Malawi, 2011–2017

Box plots show median (thick horizontal line and 25th and 75th percentiles (hinges). Whiskers represent 1.5 × interquartile range; dots show outliers.



Supplementary Figure 3. Number of specimens taken per month and number of specimens positive for each HCoV species over time among children and adults with ILI and SARI, Blantyre, Malawi (2011-2017)

Bars represent number of specimens positive for HCoVs (left y-axis). Black line and black dots show number of specimens taken (right y-axis).

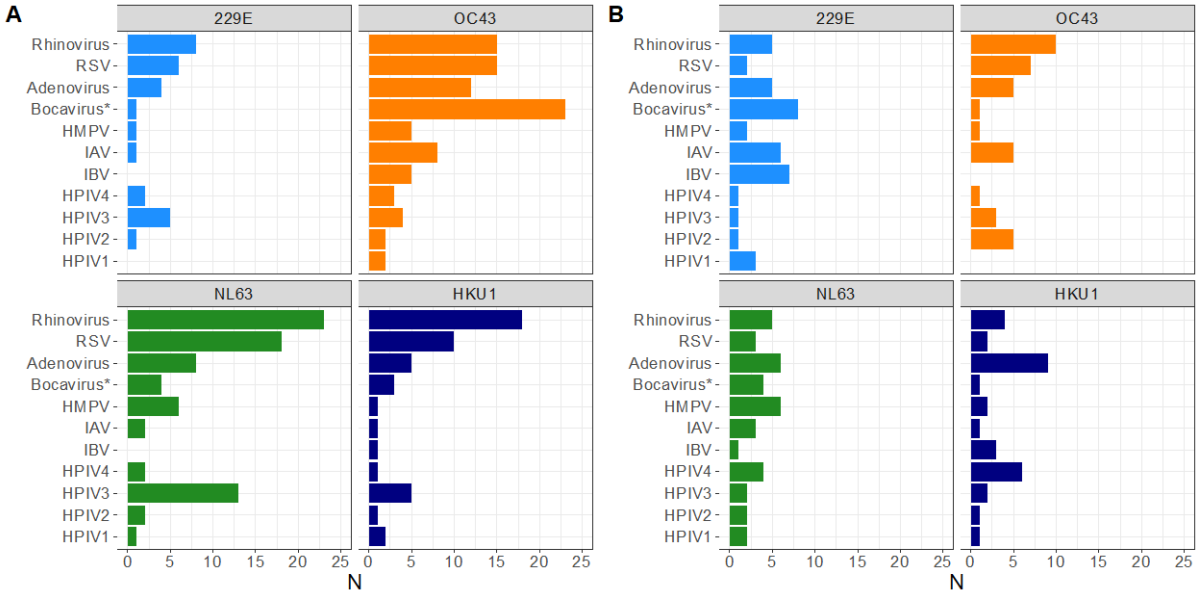

A
229E
OC43
NL63
HKU1
Rhinovirus
RSV
Adenovirus
Bocavirus*
HMPV
IAV
IBV
HPIV4
HPIV3
HPIV2
HPIV1
0
5
10
15
20
25
N
B
229E
OC43
NL63
HKU1
Rhinovirus
RSV
Adenovirus
Bocavirus*
HMPV
IAV
IBV
HPIV4
HPIV3
HPIV2
HPIV1
0
5
10
15
20
25
N
C
229E
OC43
NL63
HKU1
Rhinovirus
RSV
Adenovirus
Bocavirus*
HMPV
IAV
IBV
HPIV4
HPIV3
HPIV2
HPIV1
0
5
10
15
20
25
N

Supplementary Figure 4. Number of specimens positive for another respiratory virus among specimens positive for 229E, OC43, NL63 and HKU1 in **A)** asymptomatic controls, **B)** ILI, and **C)** SARI

Some specimens tested positive for HCoV and ≥1 other virus.

*Bocavirus results unavailable for 721 children recruited to the TAC study.

RSV, respiratory syncytial virus; HMPV, human metapneumovirus; IAV, influenza A virus; IBV, influenza B virus; HPIV, human parainfluenza virus; N, number of samples.



Supplementary Figure 5. Number of specimens positive for another respiratory virus among specimens positive for 229E, OC43, NL63 and HKU1 in **A)** children and **B)** adults

*Bocavirus results unavailable for 721 children recruited to the TAC study.

RSV, respiratory syncytial virus; HMPV, human metapneumovirus; IAV, influenza A virus; IBV, influenza B virus; HPIV, human parainfluenza virus; N, number of samples.

Supplementary Tables

Supplementary Table 1. Summary details of studies and surveillance platforms from which cases and controls were enrolled

Study	**Paediatric surveillance**[24]	**TAC**	**ARICOST**	**Infant Burden**	**Adult surveillance**[22]	**BASH-FLU**[23]
Enrolment	Cases: Children aged 3 months to 14 years meeting the SARI definition categorised according to age, primarily: 1)	Cases: Children aged <5 years, hospitalised with SARI. Controls: Outpatient children aged <5 years	Cases: Infants hospitalised with SARI were enrolled from existing paediatric surveillance studies and further consented for	Cases: IInfants aged 8 days to 11 months admitted to two hospitals (QECH and Chikwawa district hospital) enrolled by systematic	Cases: Patients presenting to QECH Emergency Department fulfilling SARI criteria: 1) an acute respiratory illness with symptom	Cases and Controls: Prospective cohort of 608 adult participants (≥18 years; n=360 (59%) HIV-infected) who attended the study clinic with ILI (cases)

	respiratory disease with signs of lower respiratory infection; 2) reported or recorded fever (>38°C); 3) symptom onset < 7 days. For a period of 1 year, ILI cases of the same age were recruited.	enrolled within 10 days of a case; not experiencing respiratory symptoms fever, diarrhoea, or other signs of infection and with no history of admission in previous 14 days, or SARI/study enrolment in previous 30 days.	detailed economic questions and a household visit at 6 weeks post discharge.	sampling (see Methods). Infants were excluded if admitted for surgery, trauma, hydrocephalus, oncology and infants with major congenital anomalies that might impact immune function will also be excluded.	onset < 7 days; 2) reported or recorded fever (>38°C); 3) cough or sore throat; and 4) shortness of breath or difficulty breathing.	or for routine visits (asymptomatic controls)

Specimen type	NPA and NP/OP swabs	NP/OP swabs	NP/OP swabs	NP/OP swabs	NPA	NP/OP swab
Number of specimens included	2181	721	294	232	1119	1560
Sex – male N (%)	1197 (54.9%)	401 (55.6%)	107 (36.4%)	144 (62.1%)	485 (43.3%)	778 (49.9%)
Age (years)						
<1	556	201	164	-	-	-
1-4	1521	515	130	-	-	-
5–14	92	5	-	-	-	-
15–39	12	-	-	-	791	1070
≥40	-	-	-	-	328	490

NP, nasopharyngeal; OP, oropharyngeal; NPA nasopharyngeal aspirate; QECH, Queen Elizabeth Central Hospital; SARI, severe acute respiratory illness,; N, number.

Supplementary Table 2. Targets for enrolment by specific respiratory pathogen surveillance studies

Study	Targets*
TAC study	10–12 cases and 5–6 controls enrolled per week
Paediatric surveillance and Infant Burden	A maximum of 15 paediatric patients, who were eligible according to either the SARI or control definition were recruited to the study per day during set recruitment hours. Recruitment would not exceed the weekly quota.
Adult surveillance	A maximum of 15 adult and 10 pregnant women who were eligible according to either the SARI or control definition were recruited to the study per day during set recruitment hours. Recruitment would not exceed the weekly quota.

SARI, severe acute respiratory illness; TAC, TaqMan Array Card

*If the expected number of cases exceeded the expected number per week, systematic sampling (e.g., every other case, enrolling 2 days on/2 days off, or in 8-hour shifts that rotate on different days) was done to ensure representativeness by epidemiology week. Eligible study participants were recruited and if the daily recruitment cap was not achieved on the day, this would be made up for on the following day.

Supplementary Table 3. Comparison of pathogens included in the TaqMan array card and FTD respiratory pathogens kit

Pathogen	TaqMan	FTD33
Adenovirus - all types	✓	✓
Bocavirus	*X*	✓
Bordetella pertussis	✓*	✓
Chlamydia pneumoniae	✓	✓
Human Enterovirus	✓	✓
Influenza A	✓	✓
Influenza B	✓	✓
Influenza C	✓	✓
Group A *Streptococcus*	✓	*X*
***Haemophilus influenzae,* all types**	✓	✓
***Haemophilus influenzae* type b**	✓	✓
Human Coronavirus (229E)	✓	✓
Human Coronavirus (NL63)	✓	✓
Human Coronavirus (OC43)	✓	✓
Human Coronavirus (HKU1)	✓	✓
Human metapneumovirus	✓	✓
Human parainfluenza virus 1	✓	✓

Human parainfluenza virus 2	✓	✓
Human parainfluenza virus 3	✓	✓
Human parainfluenza virus 4	✓	✓
Klebsiella pneumoniae	✓	✓
***Legionella* species**	✓	✓
Moraxella catarrhalis	✓	✓
Mycoplasma pneumoniae	✓	✓
Parechovirus	*X*	✓
Pseudomonas aeruginosa	✓	*X*
Pneumocystis jiroveci	✓	✓
Human rhinovirus	✓	✓
Respiratory syncytial virus	✓	✓
Staphylococcus aureus	✓	✓
Streptococcus pneumoniae	✓	✓
Mycobacterium tuberculosis	✓	*X*
Salmonella spp.	*X*	✓

*Except *Bordetella parapertussis*

Supplementary Table 4. Ethical approvals for included studies

Study	COMREC/NHSRC number	Other Institutional approval
Influenza Surveillance	COMREC P.07/10/958	Liverpool school of Tropical medicine (RETH000790)
BASH-FLU	COMREC P.11/12/1310	University of Liverpool (Study number 12.43)
TAC	COMREC P.10/12/1294	N/A
ARICOST Paediatric	NHSRC #1073	N/A
Infant Burden	COMREC P.08/16/2008	University of Liverpool (Reference 1553)

COMREC, University of Malawi College of Medicine Research Ethics Committee; NHSRC, National Health Sciences Research Committee; TAC, TaqMan array card.

Supplementary Table 5. Demographics of adult and paediatric participants who provided one or more specimens by disease severity, Queen Elizabeth Central Hospital, Blantyre, Malawi, 2011–2017 (N=6107)

		Total number of specimens N (%)*	SARI N specimens (%)	ILI** N specimens (%)	Asymptomatic Controls N specimens (%)
TOTAL		**6107**	**5045**	**345**	**717**
AGE GROUP (YEARS)	<1	2416 (39.6)	2258 (44.8)	-	158 (22.0)
	1–14	1000 (16.4)	917 (18.2)	-	83 (11.6)
	15–39	1872 (30.6)	1326 (26.3)	230 (66.7)	317 (44.2)
	≥40	819 (13.4)	544 (10.8)	115 (33.3)	159 (22.2)
SEX	Male	3112 (50.9)	2669 (52.9)	133 (38.6)	310 (43.2)
	Female	2995 (49.1)	2376 (47.1)	212 (61.4)	407 (56.8)
HIV STATUS	Negative	3075 (50.4)	2744 (54.4)	118 (34.2)	213 (29.7)
	Positive	1809 (29.6)	1319 (21.1)	227 (65.8)	263 (36.7)
	Unknown	1223 (20.0)	982 (19.5)	0 (0)	241 (33.6)
YEAR OF	2011	543 (8.9)	543 (10.8)	0 (0)	0 (0)
RECRUITMENT	2012	906 (14.8)	906 (18.0)	0 (0)	0 (0)
	2013	1905 (31.2)	1576 (31.2)	144 (41.7)	185 (25.8)
	2014	1438 (23.5)	923 (18.3)	171 (49.6)	344 (48.0)
	2015	861 (14.1)	644 (12.8)	30 (8.7)	188 (26.3)

	2016	222 (3.6)	221 (4.4)	0 (0)	0 (0)
	2017	232 (3.8)	232 (4.6)	0 (0)	0 (0)
SEASON	Hot, rainy (Dec–Mar)	1637 (26.8)	1320 (26.2)	91 (26.4)	226 (31.5)
	Cool, dry (Apr–Aug)	2909 (47.6)	2399 (47.8)	174 (50.4)	336 (46.9)
	Hot, dry (Sep–Nov)	1561 (25.6)	1326 (26.3)	80 (23.2)	155 (21.6)

HIV, human immunodeficiency virus; ILI, influenza-like illness; SARI, severe acute respiratory infection

*The specimens were collected from 5,041participants with SARI, 205 participants, and 711 asymptomatic participants,

** No data were collected on paediatric ILI.

Supplementary Table 6. Characteristics of participants with SARI, ILI, and asymptomatic control participants included in pathogen-attributable fraction analysis

	PAEDIATRIC			ADULT			
	All N=955 (%)	Asymptomatic N=241 (%)	SARI N=714 (%)	All N=1915 (%)	Asymptomatic N=476 (%)	ILI N=345 (%)	SARI N=1094 (%)
Sex							
Male	528 (55.3)	112 (46.5)	399 (55.9)	941 (49.1)	181 (38.0)	133 (38.6)	627 (57.3)
Female	427 (44.7)	129 (53.5)	315 (44.1)	974 (50.9)	295 (62.0)	212 (61.4)	467 (42.7)
HIV status							
Negative	-	-	-	674 (35.2)	213 (44.7)	118 (34.2)	343 (31.4)
Positive	-	-	-	1237 (64.6)	263 (55.3)	227 (65.8)	747 (68.3)
Missing	-	-	-	4 (0.2)	0	0	0
Season							
Hot, rainy (Dec-Mar)	244 (25.5)	59 (24.5)	185 (25.9)	453 (23.7)	167 (35.1)	91 (26.4)	195 (17.8)
Cool, dry (Apr-Aug)	540 (56.6)	123 (51.0)	417 (58.4)	937 (48.9)	213 (44.7)	174 (50.4)	550 (50.3)
Hot, dry (Sep-Nov)	171 (17.9)	59 (24.5)	112 (15.7)	525 (27.4)	96 (20.2)	30 (8.7)	349 (31.9)

ILI, influenza-like illness; SARI, severe acute respiratory illness.

*Seasonality designated using temperature and rainfall data from the Department of Climate Change and Meteorological Services, Malawi (www.metmalawi.com)