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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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SUPPLEMENTAL METHODS

Supplemental methods for Hemagglutination Inhibition

For influenza serology, hemagglutination inhibition (HI) assays were performed for both influenza A and B viruses using US CDC protocol [1]. Microneutralization (MN) assays were subsequently performed on all sera pairs that were originally positive for influenza B virus by HI assay.

For the detection of antibodies against A(H1N1)pdm09 and influenza B viruses, HI assays were performed with 0.5% turkey erythrocytes. With new antigenic clusters of A(H3N2) since 2014, the neuraminidase (NA) of these viruses have acquired the ability to bind to RBCs. Thus, for the detection of antibodies against A(H3N2) viruses, HI was conducted using 0.75% guinea pig erythrocytes in the presence of 20 nM oseltamivir carboxylate, which eliminates the interference from binding through neuraminidase.

For HI, serum samples were treated with receptor destroying enzyme and adsorbed with either turkey (for H1N1 and Bs) or guinea pig (for H3N2) erythrocytes to eliminate the nonspecific agglutinins as needed. Then Two-fold dilutions of sera with a 1:10 pre-dilution were incubated with a standard amount of virus (4HAU/25 μL), and incubated with either 0.5% turkey erythrocytes (for H1N1 and Bs), or 0.75% guinea pig erythrocytes in the presence of 20 nM oseltamivir carboxylate (for H3N2s). An HI titer was defined as the reciprocal of the highest serum dilution that completely inhibited hemagglutination. For influenza A virus HI assays, whole viruses were utilized; for influenza B virus HI assays, ether treated antigens were used to improve the assay sensitivity.

All specimens that were positive for influenza B virus in the HI assay using ether treated antigens were further tested by MN assay to verify specificity. The influenza B virus MN assays were performed by incubating two-fold serial dilutions of heat-inactivated sera (starting dilution 1:10), with 100 tissue culture infection dose 50 (TCID50) of influenza B viruses. The virus-serum mixture was then used to infect Madin-Darby canine kidney (MDCK) cells. After 18-20 hours incubation, the presence of viral protein was detected by enzyme-linked immunosorbent assay (ELISA) with a monoclonal antibody specific to the nucleoprotein of the influenza B viruses. MN titers were defined as the reciprocal of the highest dilution of serum that gave 50% neutralization.

	Representative Circulating Influenza Strains from IRIS Years (2015-16 and 2016-17)	**Assays**	
Influenza A	A/California/7/2009 (H1N1)	Turkey red blood cell (RBC) HI	
	A/Hong Kong/4801/2014 (H3N2)	GP RBC HI with 20 nM oseltamivir	
	A/Switzerland/9715293/2013 (H3N2)	GP RBC HI with 20 nM oseltamivir	
Influenza B	B/Phuket/3073/2013 (B/Yamagata)	Turkey RBC HI with ether treated antigens	MN with wild type whole virus
	B/Brisbane/60/2008(B/Victoria)	Turkey RBC HI with ether treated antigens	MN with wild type whole virus

Supplemental methods for variable imputation

A small number of variable values were imputed using regression methods. A combination of key variables (country, infant age, study year and material depravation) was used to linearly impute missing values for five covariates. A linear regression model was run to predict observed values for each covariate. The linear regression model was then used to systematically impute missing values for each covariate with missing values. For this manuscript the only variable that required imputation was parent-reported infant health; 2.2% of the analytic sample had missing values for this variable and were imputed. Imputation procedures were conducted using SPSS statistical software (IBM). Imputation by regression biases results toward the null, as imputed values fit perfectly along the regression line without incorporating residual variance.

Supplemental methods for statistical analyses

Enrollment and data collection was managed using REDCap (Research Electronic Data Capture) (Vanderbilt University, Nashville, TN) [2].

For this analysis, a modified WHO SARI case definition was used to define SARI case definition at admission. Infants with either: a measured fever of ≥ 38° C, reported fever at admission or reported chills at admission and reported cough at admission were classified as SARI at admission. All infants enrolled in the study had illness onset within 10 days, which also meets the WHO SARI case definition.

Discharge diagnoses were classified as "respiratory" or "non-respiratory" based on written discharge diagnosis that were abstracted by trained study staff. For all infants with multiple discharge diagnoses, infants with both respiratory and non-respiratory diagnoses were classified as "respiratory': infants with at least one non-respiratory diagnosis and no respiratory diagnoses were classified as "non-respiratory." For four infants who were missing a written discharge diagnosis, the International Classification of Disease (ICD) codes assigned by hospital administration were referenced in order to make the classification.

The proportions of infants classified as non-SARI at admission and infants with a non-respiratory discharge diagnosis with 95% confidence intervals were calculated among infants testing positive for influenza using rRT-PCR by study year, study site and infant age assuming a binomial distributions.

Our main study outcome is the ratio of influenza-positives (by either rRT-PCR or seroconversion) with any clinical diagnosis to rRT-PCR-confirmed influenza-positives with respiratory diagnoses. We wished to calculate a summary statistic that pooled the estimate of this ratio across study sites and influenza seasons. Pooling all observations into one binomial estimate has limitations, since it would assume that the true ratio is fixed across sites and seasons. However, we expected that the true ratio could vary by site and influenza season for multiple reasons, including differences in the age composition of enrolled patients, the frequency of acute respiratory vs. non-respiratory disease, and the (sub)types of circulating influenza viruses. Pooling validly heterogeneous results across sites assuming a

binomial distribution creates over-dispersion of the data and as a result can lead to erroneous estimates and confidence intervals for the outcomes of interest. Specifically, underestimation of standard error in a pooled estimate that incorrectly assumes a common binomial distribution increases the chance of Type I error.

In contrast, in a beta-binomial model, the true value of the ratio is not assumed to be fixed across studies, sites, or years but is a random (varying) effect that follows a beta distribution. A detailed explanation of the beta-binomial model and the process of estimating pooled proportions or ratios is previously published by Young-Xu et al. [3]. This approach has also emerged as the preferred method for combining multiple surveillance data sources in the United States in order to estimate seasonal influenza disease burden [3, 4].

For the ratios presented in Table 4, we applied beta-binomial models with maximum likelihood estimation to obtain pooled proportions using the SAS macro BETABIN. Using the procedure SAS procedure NLMIXED, this macro provides maximum likelihood estimates of the mean and standard deviation from each distribution [4]. All analyses were conducted using SAS 9.4 (Cary, NC).

Supplemental References

1. Network WHOGIS. Serological diagnosis of influenza by haemagglutination inhibition testing. In: Manual for the laboratory diagnosis and virological surveillance of influenza. Geneva, Switzerland: WHO, **2011**:59-62.

2. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform **2009**; 42:377-81.

3. Young-Xu Y, Chan KA. Pooling overdispersed binomial data to estimate event rate. BMC medical research methodology **2008**; 8:58.

4. Reed C, Chaves SS, Daily Kirley P, et al. Estimating influenza disease burden from population-based surveillance data in the United States. PloS one **2015**; 10:e0118369.

Supplemental Table A. Network study countries, sponsors, and enrollment sites

City, Country (Local Population Served by Hospitals)	Sponsoring Institution	Reference Laboratory (WHO National Influenza Centers)[A,B]	Hospitalized Infant Study			Non-Ill Infant Study
			Study Hospitals	Number of Pediatric General Ward Beds	Number of Pediatric Intensive Care Beds	Non-Ill Enrollment Sites
Tirana, Albania (~610,000)	South East European Center for Surveillance & Control of Infectious Diseases	Institute of Public Health Tirana	Pediatric Department University Hospital "Mother Theresa"	88	25	Enrolled during well-baby immunization visits to (a) Mother and Child Consultancy Room, Health Center No. 4 Tirana, Tirana Regional Health Authority, and (b) the Pediatric Surgical Ward, University Hospital "Mother Theresa," Tirana, Albania
			Maternity Hospital "Queen Geraldine" Neonatology Unit	19	5	
Amman, Jordan (~4 Million)	The Eastern Mediterranean Public Health Network	Central Public Health Laboratory Jordan	Al-Basheer Hospital, Maternal and Pediatric Building	120	70	Enrolled from Al-Owdah Primary Healthcare Center, which provides maternal and child health services; infants are recruited during routine visits for immunization, growth monitoring, or other well-baby check-ups
Managua, Nicaragua (~1 Million)	Sustainable Sciences Institute	Centro Nacional de Diagnostico y Referencia (CNDR)	Hospital Infantil Manual De Jesus Rivera "La Mascota"	270	31	Enrolled from Health Center Socrates Flores Vivas during immunization visits and from a local pediatric cohort study
Bohol Island, The Philippines (~1.4 Million)	Research Institute for Tropical Medicine	Research Institute for Tropic Medicine	Governor Celestino Gallares Memorial Regional Hospital	42	8	Enrolled during immunization visits at (a) Cogon Lower Barangay Health Station, (b) Cogon Upper Barangay Health Station, and (c) Taloto Health

[A]Respiratory specimens were tested for influenza using validated singleplex rRT-PCR assays, with protocols, primers, probes, and reagents supplied by US CDC International Reagent Resource (IRR).

[B]Study laboratories completed influenza proficiency panels in both years and quality assurance testing (of every 5th influenza-positive and every 20th influenza-negative) in the first year administered by Marshfield Clinic Laboratory (Marshfield, Wisconsin).

Supplemental Table B. Influenza Virus Cirulation by WHO Influenza Transmission Zone during IRIS Enrollment Periods.

	IRIS Network Enrollment			WHO International Surveillance								
	Total Enrollment Period	Influenza Season Enrollment Period	No. Influenza Season Weeks	WHO Transmission Zone[A]	Total # Positive Specimens	# Positive A(H1N1)pdm09 (%)	# Positive A(H3N2) (%)	# Positive A(not subtyped) (%)	# Positive B (Yamagata) (%)	# Positive B (Victoria) (%)	# Positive B (lineage not determined) (%)	Climate[G]
Year 1												
Albania	Week 47, 2015 - Week 17, 2016	Week 7, 2016 - Week 17, 2016	11	South West Europe[B]	44589	14785 (33%)	1711 (4%)	8139 (18%)	186 (0.4%)	4496 (10%)	15272 (34%)	Temperate
Nicaragua	Week 25, 2015 - Week 4, 2016	Week 46, 2015 - Week 52, 2015	7	Central America Caribbean[C]	2534	1341 (53%)	1013 (40%)	43 (2%)	36 (1%)	4 (0.2%)	94 (4%)	Tropical
Jordan	Week 51, 2015 - Week 17, 2016	Week 51, 2015 - Week 16, 2016	18	Western Asia[D]	14265	7734 (54%)	2725 (19%)	541 (4%)	75 (0.5%)	32 (0.2%)	3158 (22%)	Temperate
Year 2												
Albania	Week 43, 2016 - Week 15, 2017	Week 49, 2016 - Week 12, 2017	16	South West Europe[B]	58839	187 (0.3%)	22851 (39%)	33054 (56%)	545 (1%)	101 (0.2%)	2101 (4%)	Temperate
Nicaragua	Week 20, 2016 - Week 8, 2017	Week 40, 2016 - Week 2, 2017	15	Central America Caribbean[C]	5231	2873 (55%)	1138 (22%)	66 (1%)	257 (5%)	95 (2%)	802 (15%)	Tropical
Jordan	Week 45, 2016 - Week 15, 2017	Week 45, 2016 - Week 1, 2017	9	Western Asia[D]	5969	326 (5%)	2165 (36%)	1978 (33%)	71 (1%)	87 (1%)	1342 (22%)	Temperate
Both Years												
Philippines[F]	Week 39, 2015 - Week 51, 2016	Week 17, 2016 - Week 50, 2016	34	South East Asia[E]	6649	1491 (22%)	2155 (32%)	23 (0.3%)	322 (5%)	992 (15%)	1665 (25%)	Tropical

[A]All IRIS countries (Albania, Nicaragua, Jordan and the Philippines) contributed to the GISRS network during the reporting periods listed.

[B]**Countries in South West Europe**: Albania, Andorra, Austria, Belgium, Bosnia and Herzegovina, Croatia, France, Germany, Gibraltar, Greece, Italy, Luxembourg, Malta, Midway Islands, Monaco, Montenegro, Netherlands, Portugal, San Marino, Serbia, Slovenia, Spain, Switzerland, The former Yugoslav Republic of Macedonia.

[C]**Countries in Central America Caribbean Transmission Zone:** Anguilla, Antigua and Barbuda, Aruba, Bahamas, Barbados, Belize, British Virgin Islands, Cayman Islands, Costa Rica, Cuba, Dominica, Dominican Republic, El Salvador, Grenada, Guadeloupe, Guatamala, Haiti, Honduras, Jamaica, Martinique, Mexico, Monteserrat, Netherlands Antilles, Nicaragua, Puerto Rico, Panama, Puerto Rica, Saint Kitts and Nevis, Saint Lucia, Saint Vincent and the Grenadines, Trinidad and Tobego, Turks and Caicos Islands, United States Virgin Islands.

[D]**Countries in Western Asia:** Armenia, Azerbaijan, Bahrain, Cyprus, Georgia, Iraq, Israel, Jordan, Kuwait, Lebanon, Oman, Qatar, Saudi Arabia, Syrian Arab Republic, Turkey, United Arab Emirates, West Bank and Gaza Strip, Yemen.

[E]**Countries in South East Asia:** Brunei Darussalam, Cambodia, Indonesia, Lao People's Democratic Republic, Malaysia, Myanmar, Philippines, Singapore, Thailand, Timor-Leste, Viet Nam.

[F]For the period of the IRIS study the Philippines was treated as one continuous season/reporting period, and this table reflects that information.

[G]Climate for each country was determined using the lattitude of the city where the study was conducted: Tirana, Albania; Managua, Nicaragua; Amman, Jordan; Manila, Philippines. Countries were classified as temperate if lattitude >|30°|, sub-tropical if lattitude |23.6-29°| and tropical if lattitude ≤|23.5°|

Supplemental_Table_C. Number and percentage of consented infants versus those not consented due to parental refusal to participate in sceening or enroll by study year, site, and infant characteristics.

	Consented Eligible Infants		Refused Consent to Screening or Enrollment			
	N	(Row %)	N	(Row %)	Bivariate p-value[a]	Multivariable Odds Ratio (95% CI)	p-value[b]
All sites	3634	(91)	375	(9)			
Enrollment Year					<0.0001		
Year 1	1821	(88)	237	(12)		REF	
Year 2	1813	(93)	138	(7)		1.29 (1.02 - 1.62)	0.030
Enrollment Site					<0.0001		
Albania	1032	(97)	31	(3)		10.38 (6.95 - 15.51)	<0.0001
Jordan	1057	(94)	63	(6)		5.61 (4.07 - 7.73)	0.0006
Nicaragua	937	(92)	86	(8)		3.37 (2.55 - 4.45)	0.330
Philippines	608	(76)	195	(24)		REF	
Age Categories					0.18		
0-2 months	1794	(91)	187	(9)		0.79 (0.57 - 1.11)	0.080
3-5 months	707	(92)	58	(8)		1.10 (0.74 - 1.64)	0.160
6-8 months	595	(89)	73	(11)		0.86 (0.59 - 1.26)	0.480
9-11 months	538	(90)	57	(10)		REF	
Infant Sex					0.21		
Male	2099	(91)	204	(9)		REF	
Female	1535	(90)	171	(10)		0.81 (0.65 - 1.01)	0.060
Hospital Placement					0.04		
General Ward	2710	(90)	298	(10)		REF	
ICU or Requires ICU	924	(92)	77	(8)		1.10 (0.81 - 1.50)	0.550

[a]P-values of Chi-square test of differences between consented eligible infants and infants that refused consent to screening or enrollment.

[b]P-values are associated with the adjusted beta coefficients, from which the odds ratios are derived, from a logistic regression model with consented versus not as the outcome and all covariates included simultaneously.

Supplemental_Table_D. Number and percentage of infants with complete acute and convalescent sera pairs versus those exluded due to lack of convalescent sera by study year, site, and infant characteristics.

	Complete Sera Pairs		Excluded due to Lack of Complete Sera		Bivariate p-value[a]	Multivariable Odds Ratio (95% CI)	p-value[b]
	N	(Row %)		(Row %)			
All sites	1943	(86)	315	(14)			
Enrollment Year					0.05		
Year 1	937	(85)	171	(15)		REF	
Year 2	1006	(87)	144	(13)		1.30 (1.00 - 1.70)	0.050
Enrollment Site					<0.0001		
Albania	638	(93)	47	(7)		4.99 (3.37 - 7.38)	<0.0001
Jordan	664	(92)	54	(8)		5.68 (3.89 - 8.32)	<0.0001
Nicaragua	307	(77)	93	(23)		1.12 (0.81 - 1.56)	<0.0001
Philippines	334	(73)	121	(27)		REF	
Age Categories					0.90		
0-2 months	988	(86)	156	(14)		0.71 (0.48 - 1.07)	0.350
3-5 months	364	(85)	62	(15)		0.68 (0.43 - 1.06)	0.260
6-8 months	328	(85)	57	(15)		0.77 (0.49 - 1.21)	0.930
9-11 months	263	(87)	40	(13)		REF	
Infant Sex					0.08		
Male	1121	(85)	198	(15)		REF	
Female	822	(88)	117	(12)		1.16 (0.90 - 1.50)	0.250
Hospital Placement					0.06		
General Ward	1403	(85)	239	(15)		1.55 (1.11 - 2.15)	0.020
ICU or Requires ICU	540	(88)	76	(12)		REF	
Discharge Diagnosis					<0.0001		
Respiratory	1911	(93)	152	(7)		REF	
Non-Respiratory	752	(82)	163	(18)		0.66 (0.51 - 0.85)	0.002
Flu PCR Results					0.90		
Negative	1791	(86)	291	(14)		REF	
Positive	152	(86)	24	(14)		0.77 (0.48 - 1.24)	0.290

[a]P-values of Chi-square test of differences between the analytic sample and those excluded due to lack of complete sera pairs.

[b]P-values are associated with the adjusted beta coefficients, from which the odds ratios are derived, from a logistic regression model with complete sera pairs versus not as the outcome and all covariates included simultaneously.

Supplemental Table E. Sensitivity and Specificity of rRT-PCR and Serology among various groups.

	≥4-fold antibody increase (to GMT ≥40)						rRT-PCR-Confirmed to Serologic-Confirmed Influenza [Serology Gold Standard]				Serologic-Confirmed to rRT-PCR-Confirmed Influenza [rRT-PCR Gold Standard]			
	Negative			Positive										
		Row %	Col %		Row %	Col %	Sensitivity	95% CI	Specificity	95% CI	Sensitivity	95% CI	Specificity	95% CI
All ages (n=1943)							48%	(41 - 55)	97%	(96 - 98)	62%	(54 - 70)	94%	(93 - 95)
rRT-PCR Influenza Results														
Negative	1689	94	97	102	6	52								
Positive	58	38	3	94	62	48								
0 - 5 Months (n=1352)							38%	(29 - 47)	97%	(96 - 98)	50%	(39 - 61)	95%	(94 - 96)
rRT-PCR Influenza Results														
Negative	1206	95	97	66	5	62								
Positive	40	50	3	40	50	38								
6-11 Months (n= 591)							60%	(51 - 71)	96%	(94 - 98)	75%	(65 - 85)	93%	(91 - 95)
rRT-PCR Influenza Results														
Negative	483	93	96	36	7	40								
Positive	18	25	4	54	75	61								
A(H1N1)pdm09 (n=1943)							50%	(36 - 64)	99.7%	(99 - 100)	82%	(68 - 96)	99%	(99 - 99)
rRT-PCR Influenza Results														
Negative	1892	99	100	23	1	50								
Positive	5	18	0	23	82	50								
A(H3N2) (n=1943)							39%	(29 - 47)	98%	(97 - 99)	56%	(47 - 69)	96%	(95 - 97)
rRT-PCR Influenza Results														
Negative	1807	97	98	63	3	61								
Positive	32	44	2	41	56	39								
B viruses (n=1943)							64%	(53 - 81)	99%	(99 - 99)	61%	(47 - 75)	99%	(99 - 99)
rRT-PCR Influenza Results														
Negative	1881	99	99	16	1	36								
Positive	18	39	1	28	61	64								

Supplemental Table F. Demographic and Health Characteristics of Non-ill Infants by Study Site (N=745).

	Non-ill Cohort		Albania		Jordan		Nicaragua		Philippines	
	N	(col. %)	N	(col. %)	N	(col. %)	N	(col. %)	N	(col. %)
All Infants	745		277		210		180		78	
Infant Age										
Age Dichotomous										
0-5 months	496	(67)	176	(64)	137	(65)	118	(66)	65	(83)
6-11 months	249	(33)	101	(36)	73	(35)	62	(34)	13	(17)
Age Categories										
0-2 months	313	(42)	102	(37)	75	(36)	82	(46)	54	(69)
3-5 months	183	(25)	74	(27)	62	(30)	36	(20)	11	(14)
6-8 months	103	(14)	53	(19)	10	(5)	36	(20)	4	(5)
9-11 months	146	(20)	48	(17)	63	(30)	26	(14)	9	(12)
Other Infant Characteristics										
Setting										
Study Year										
Year 1	345	(46)	123	(44)	113	(54)	54	(30)	55	(71)
Year 2	400	(54)	154	(56)	97	(46)	126	(70)	23	(29)
Infant Sex										
Male	405	(54)	167	(60)	99	(47)	85	(47)	54	(69)
Female	340	(46)	110	(40)	111	(53)	95	(53)	24	(31)
Infant Health by Parent Report										
Clinical Preterm and GA <37 Weeks[b]	16	(2)	8	(3)	2	(1)	4	(2)	2	(3)
Chronic Medical Condition(s)[c]	27	(4)	11	(4)	11	(5)	2	(1)	3	(4)
Prior Hospitalization[d]	43	(6)	13	(5)	5	(2)	13	(7)	12	(15)
Parent Reported Infant Health[e]										
Poor/Fair	10	(1)	4	(1)	2	(1)	0	(0)	4	(5)
Good	158	(21)	34	(12)	24	(11)	84	(47)	16	(21)
Excellent/Very Good	577	(77)	239	(86)	184	(88)	96	(53)	58	(74)
Influenza vaccination										
Mother vaccinated during pregnancy	99	(13)	0	(0)	0	(0)	98	(54)	1	(1)
Infant vaccinated ≥6 months	3	(0)	0	(0)	0	(0)	2	(1)	1	(1)

No influenza vaccination	643	(	86	)	277	(	100	)	210	(	100	)	80	(	44	)	76	(	97	)
Influenza Outcomes																			
rRT-PCR Influenza																			
Negative	724	(	97	)	272	(	98	)	199	(	95	)	175	(	97	)	78	(	100	)
A or B Positive	21	(	3	)	5	(	2	)	11	(	5	)	5	(	3	)	0	(	0	)
A Positive[h]	18	(	86	)	5	(	100	)	9	(	82	)	4	(	80	)	0	(	0	)
A(H1N1)pdm09 Positive[i]	3	(	17	)	0	(	0	)	0	(	0	)	3	(	75	)	0	(	0	)
A(H3N2) Positive[i]	13	(	72	)	3	(	60	)	9	(	100	)	1	(	25	)	0	(	0	)
B Positive[h]	3	(	14	)	0	(	0	)	2	(	18	)	1	(	20	)	0	(	0	)
B (Victoria) Positive[j]	2	(	67	)	0	(	0	)	2	(	100	)	0	(	0	)	0	(	0	)
B (Yamagata) Positive[j]	0	(	0	)	0	(	0	)	0	(	0	)	0	(	0	)	0	(	0	)

significant difference between sites (p-value > 0.05).

[b]Not preterm includes infants with known gestational age >37 weeks, and parental reported "no" for infants with gestational age < 37 weeks.

[c]No chronic conditions reported includes unknown/refused (n=40).

[d]Not confirmed by parent includes those that are missing, refused or unknown (n=46).

[e] Two percent with missing values were imputed as a linear function of infant age, country, study year and other demographic variables.

[g]General ward includes category "required ICU but placed in general ward".

[h]Denominator is out of total positives, A or B by RT-PCR.

[i]Denominator is out of influenza A positives, including those that could not be subtyped.

[j]Denominator is out of influenza B positves, including those with indeterminate lineage.

Supplemental Table G. Demographics by PCR confirmed influenza, nonill sample (N=745).

	Flu Outcomes							
	Negative		Positive			Percent Positive		
	N	(Col %)	N	(Col. %)	p-value	(Row %)	(95% CI)	
All Infants	724		21			(2.8)	(1.6 - 4.0)	
Infant Age								
Age Dichotomous					0.25			
0-5 months	485	(67)	11	(52)		(2.2)		
6-11 months	239	(33)	10	(48)		(4.0)		
Age Categories					0.37			
0-2 months	308	(43)	5	(24)		(1.6)		
3-5 months	177	(24)	6	(29)		(3.3)		
6-8 months	99	(14)	4	(19)		(3.9)		
9-11 months	140	(19)	6	(29)		(4.1)		
Other Infant Characteristics								
Enrollment Year					0.10			
Year 1	339	(47)	6	(29)		(1.7)		
Year 2	385	(53)	15	(71)		(3.8)		
Enrollment Site					0.05			
Albania	272	(38)	5	(24)		(1.8)	(0.2 - 3.4)	
Jordan	199	(27)	11	(52)		(5.2)	(2.2 - 8.3)	
Nicaragua	175	(24)	5	(24)		(2.8)	(0.4 - 5.2)	
Philippines	78	(11)	0	(0)		(0.0)	(0.0 - 0.0)	
Infant Sex					0.48			
Male	392	(54)	13	(62)		(3.2)		
Female	332	(46)	8	(38)		(2.4)		
Infant Health by Parent Report								
Clinical Preterm and GA <37 Weeks[c]	16	(2)	0	(0)	0.55	(0.0)		
Chronic Medical Condition(s)[d]	19	(3)	0	(0)	0.67	(0.0)		
Prior Hospitalization[e]	43	(6)	34	(162)	0.49	(44.2)		
Parent Reported Infant Health[f]					0.83			
Poor/Fair	10	(1)	0	(0)		(0.0)		
Good	154	(21)	4	(19)		(2.5)		

Excellent/Very Good	560	(	77	)	17	(	81	)		(	2.9	)
Influenza Outcomes												
A Influenza Positive	--		--		18	(	86	)				
A(H1N1)pdm09 Positive	--		--		3	(	17	)				
A(H3N2) Positive	--		--		13	(	72	)				
B Influenza Positives	--		--		3	(	14	)				
B (Victoria) Positive	--		--		2	(	67	)				
Follow-up interview (Year 2 only)	385	(	53	)	15	(	71	)		(	3.8	)
Days since enrollment interview, mean days (SD)	7.5	(	2.3	)	6.5	(	2.0	)				
Symptoms in past 7 days												
Any symptom	70	(	18	)	4	(	27	)	0.41	(	5.4	)
Congestion/Runny nose	44	(	11	)	3	(	20	)	0.32	(	6.4	)
New or worstening cough	30	(	8	)	2	(	13	)	0.44	(	6.3	)
Difficulty breathing	8	(	2	)	0	(	0	)	0.77	(	0.0	)
Wheezing	5	(	1	)	0	(	0	)	0.63	(	0.0	)
Fever	17	(	4	)	1	(	7	)	0.69	(	5.6	)
Chills	1	(	0	)	0	(	0	)	0.84	(	0.0	)
Diarrhea	10	(	3	)	1	(	7	)	0.35	(	9.1	)

[a]Not confirmed by parent includes those that are missing, refused or unknown (n=46).

[b]Not preterm includes infants with known gestational age >37 weeks, and parental reported "no" for infants with gestational age < 37 weeks.

[c]In addition to mother and infant.

[d]Confirmed by parent, or unconfirmed (no includes unknown and missing, n=7).

[e]No includes Unknown, refused, missing (n=11).

[f]Combination of lack of electricity, private indoor flush toilet or private indoor water sealed toilet, and earth floor.

[g]Temperature measured at or above 39 degrees celcius.

[h]For infants aged 0-2 months, respiration rate >60 breaths/minute, for infants aged 2-12 months, respiration rate >50 breaths/minute.

[i]Measured oxygen saturation less than 93%.

Supplemental Table H. Influenza virus positives by SARI case definition at admission and percentage of all influenza positives with a non-SARI case definition at admission (n=254).

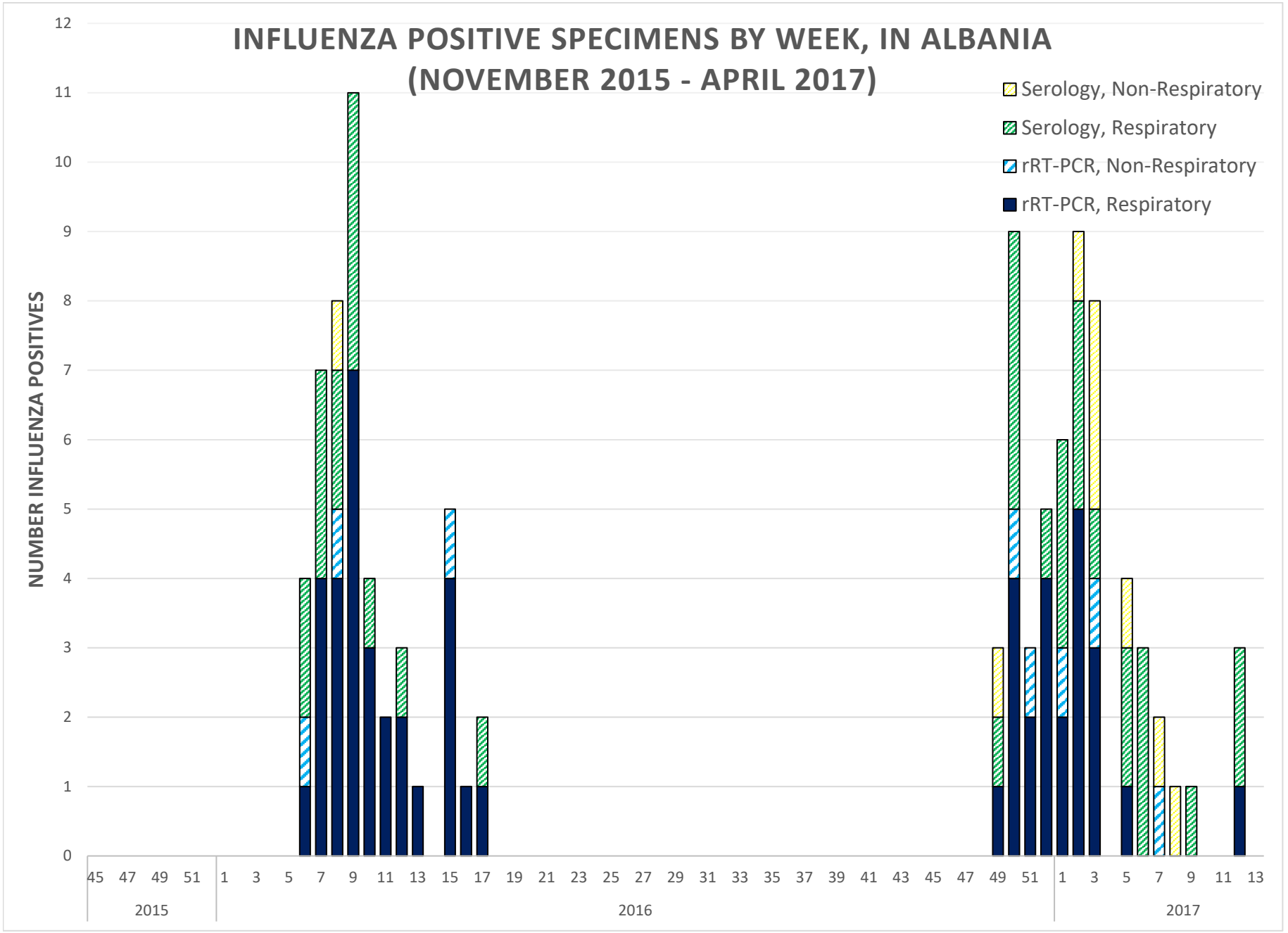
	SARI at Admission (A)		Non-SARI at Admission (B)		Percentage (%) of All Influenza Positives non-SARI		Under-Detection Multiplier[a] [Pooled by Site & Year]	
	N	(Col %)	N	(Col %)	%	(95% CI)	N	(95% CI)
All Infants	157		97		38	(32 - 44)	2.6	(2.0 - 3.5)
Infant Age								
Age Dichotomous								
0-5 months	82	(52)	64	(66)	44	(36 - 52)		
6-11 months	75	(48)	33	(34)	31	(22 - 39)		
Age Categories								
0-2 months	42	(27)	45	(46)	52	(41 - 62)		
3-5 months	40	(25)	19	(20)	32	(20 - 44)		
6-8 months	50	(32)	15	(15)	23	(13 - 33)		
9-11 months	25	(16)	18	(19)	42	(27 - 57)		
Other Infant Characteristics								
Enrollment Year								
Year 1	78	(50)	44	(45)	36	(28 - 45)		
Year 2	79	(50)	53	(55)	40	(32 - 49)		
Enrollment Site								
Albania	75	(48)	30	(31)	29	(20 - 37)		
Jordan	41	(26)	46	(47)	53	(42 - 63)		
Nicaragua	17	(11)	14	(14)	45	(28 - 63)		
Philippines	24	(15)	7	(7)	23	(8 - 37)		
Infant Sex								
Male	98	(62)	44	(45)	31	(23 - 39)		
Female	59	(38)	53	(55)	47	(38 - 57)		
Index Illness								
Days since onset								
0-3 days	88	(56)	64	(66)	42	(34 - 50)		
4-10 days	69	(44)	33	(34)	32	(23 - 41)		

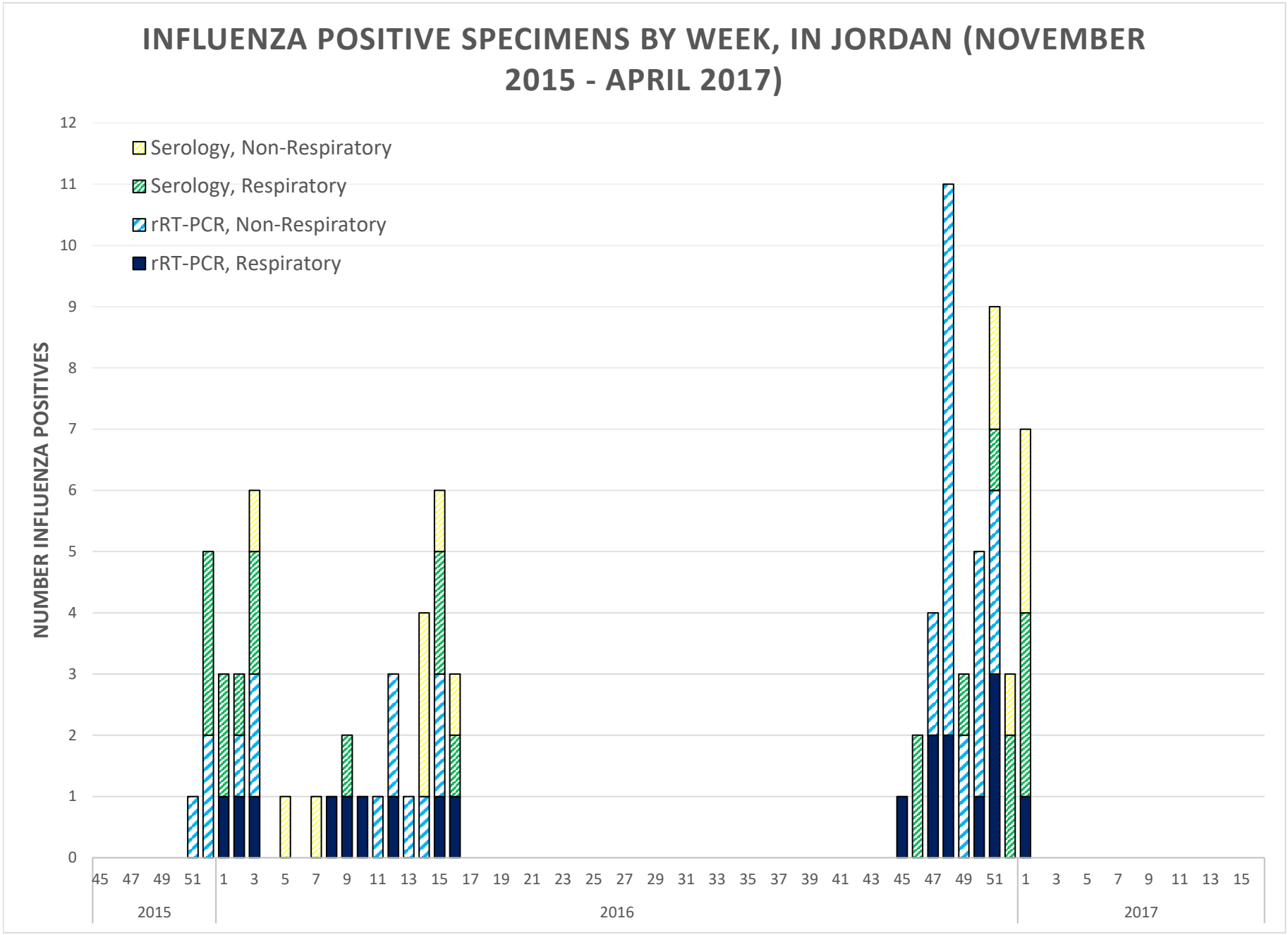
Days since onset, Mean (SD)	3.6	(	1.8	)	3.0	(	1.9	)					
Hospital Placement[h]													
General Ward (GW)	131	(	83	)	66	(	68	)	34	(	27	-	40)
Intensive Care Unit (ICU)	26	(	17	)	31	(	32	)	54	(	41	-	67)
Influenza Outcomes (PCR and/or Sero)													
A Influenza Positive	118	(	75	)	80	(	82	)	40	(	34	-	47)
A(H1N1)pdm09 Positive	35	(	22	)	16	(	16	)	31	(	19	-	44)
A(H3N2) Positive	80	(	51	)	63	(	65	)	44	(	36	-	52)
B Influenza Positives	43	(	27	)	19	(	20	)	31	(	19	-	42)
B (Victoria) Positive	40	(	25	)	17	(	18	)	30	(	18	-	42)

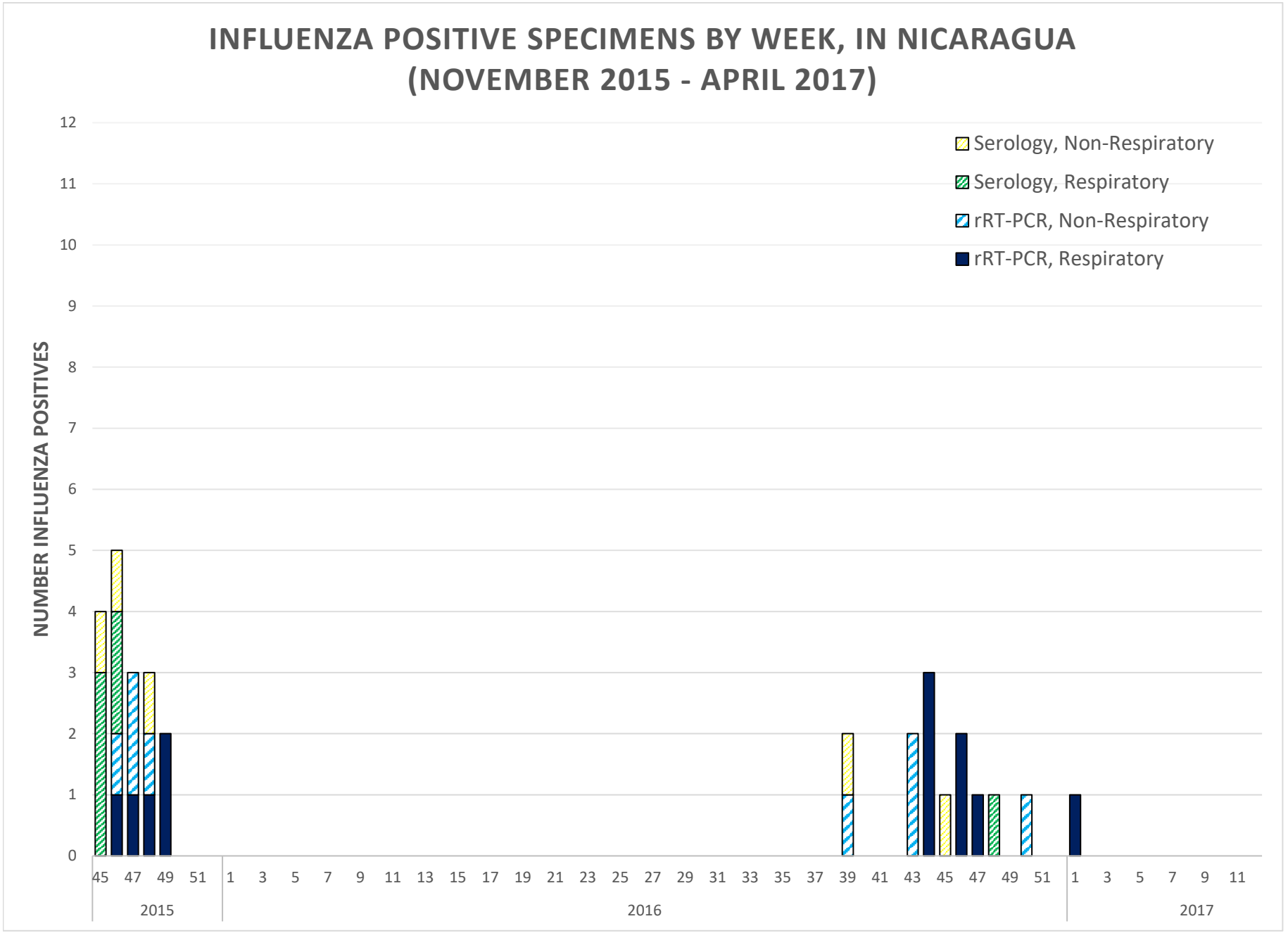
[a]Pooled estimates accounting for site and year calculated using beta binomial models with maximum likelihood estimation

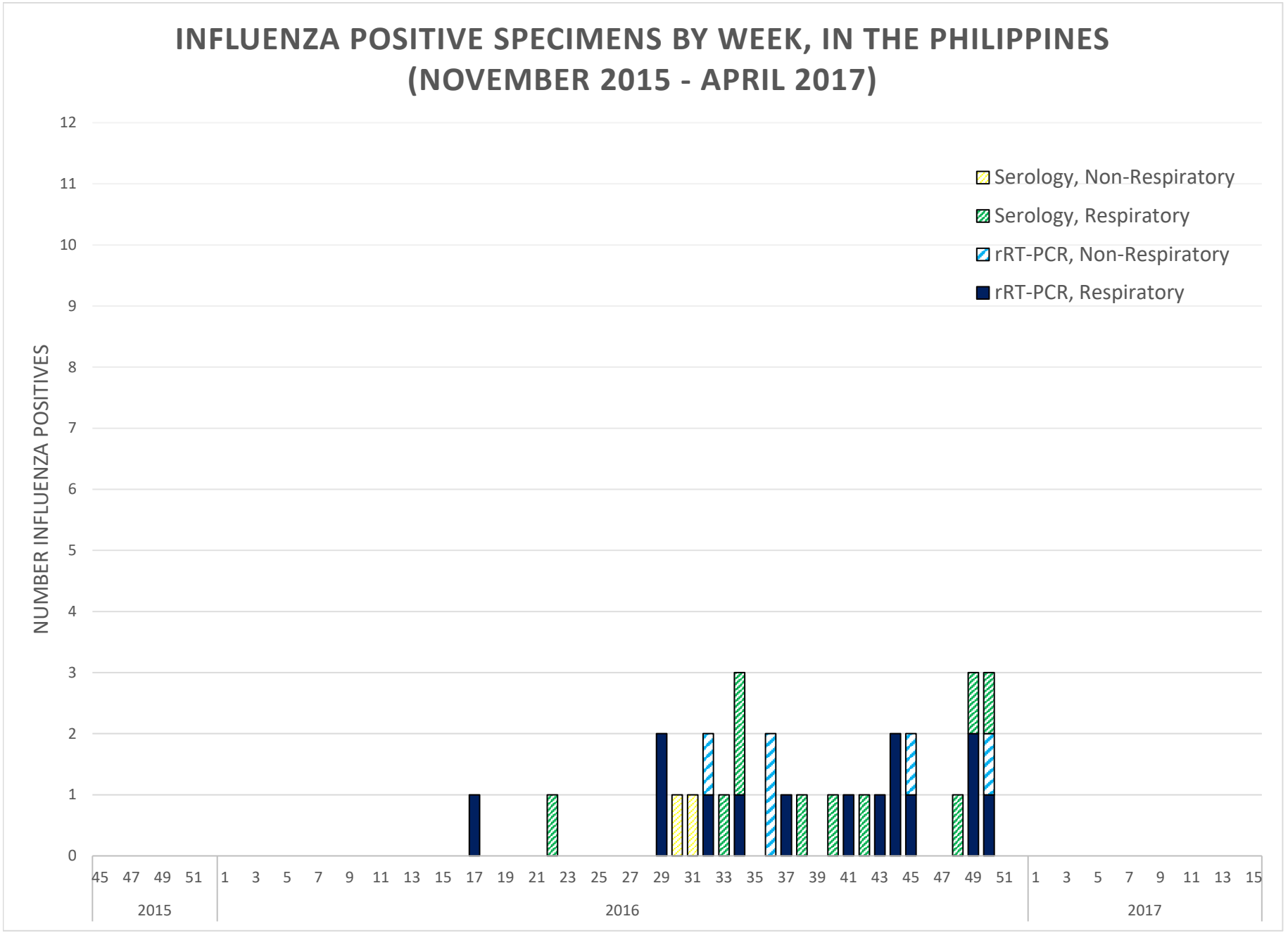
Supplemental Table J. Cross-tabulation of rRT-PCR by Serology Results and Admission by Discharge Diagnoses.

	≥4-fold antibody increase (to GMT ≥40)				Sample	
	Negative		Positive			
	(Row %)		(Row %)		N	(Col %)
rRT-PCR Influenza Results						
Negative	1689	(94)	102	(6)	1791	(92)
Positive	58	(38)	94	(62)	152	(8)
Sample (Row %)	1747	(90)	196	(10)	1943	(100)
	Clinical Discharge Diagnosis				**Sample**	
	Respiratory		Non-Respiratory			
	(Row %)		(Row %)		N	(Col %)
Any Complaint at Admission						
Respiratory	1099	(95)	58	(5)	1157	(60)
Non-Respiratory	92	(12)	694	(98)	786	(40)
Sample (Row %)	1191	(61)	752	(39)	1943	(100)
	Clinical Discharge Diagnosis				**Sample**	
	Respiratory		Non-Respiratory			
	(Cell %)		(Cell %)		N	(Cell %)
Any Complaint at Admission						
Respiratory	87/1099	(8)	1/58	(2)	88/1157	(8)
Non-Respiratory	11/92	(12)	53/694	(8)	64/786	(8)
Sample (Cell %)	98/1191	(8)	54/752	(7)	152/1943	(8)


INFLUENZA POSITIVE SPECIMENS BY WEEK, IN ALBANIA
(NOVEMBER 2015 - APRIL 2017)
NUMBER INFLUENZA POSITIVES
Serology, Non-Respiratory
Serology, Respiratory
rRT-PCR, Non-Respiratory
rRT-PCR, Respiratory
0
1
2
3
4
5
6
7
8
9
10
11
12
45 47 49 51 1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31 33 35 37 39 41 43 45 47 49 51 1 3 5 7 9 11 13
2015
2016
2017


INFLUENZA POSITIVE SPECIMENS BY WEEK, IN JORDAN (NOVEMBER 2015 - APRIL 2017)
Serology, Non-Respiratory
Serology, Respiratory
rRT-PCR, Non-Respiratory
rRT-PCR, Respiratory
NUMBER INFLUENZA POSITIVES
0
1
2
3
4
5
6
7
8
9
10
11
12
45 47 49 51 1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31 33 35 37 39 41 43 45 47 49 51 1 3 5 7 9 11 13 15
2015
2016
2017


INFLUENZA POSITIVE SPECIMENS BY WEEK, IN NICARAGUA
(NOVEMBER 2015 - APRIL 2017)
NUMBER INFLUENZA POSITIVES
Serology, Non-Respiratory
Serology, Respiratory
rRT-PCR, Non-Respiratory
rRT-PCR, Respiratory
0
1
2
3
4
5
6
7
8
9
10
11
12
45 47 49 51 1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31 33 35 37 39 41 43 45 47 49 51 1 3 5 7 9 11
2015
2016
2017


INFLUENZA POSITIVE SPECIMENS BY WEEK, IN THE PHILIPPINES
(NOVEMBER 2015 - APRIL 2017)
NUMBER INFLUENZA POSITIVES
0
1
2
3
4
5
6
7
8
9
10
11
12
Serology, Non-Respiratory
Serology, Respiratory
rRT-PCR, Non-Respiratory
rRT-PCR, Respiratory
45 47 49 51 1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31 33 35 37 39 41 43 45 47 49 51 1 3 5 7 9 11 13 15
2015
2016
2017

Supplemental Table K. Participant Enrollment and Consent by Study Site.

	All Study Sites	Albania	Jordan	Nicaragua	Philippines
Enrollment and consent steps					
Infants potentially eligible from chart review	4031	1063	1134	1031	803
Refused screening questions	*<112>*	*<3>*	*<54>*	*<52>*	*<3>*
Infants completed screening	3919	1060	1080	979	800
Excluded due to illness onset >10 days	*<22>*	*<0>*	*<14>*	*<8>*	*<0>*
Eligible infants	3897	1060	1066	971	800
Refused consent and/or enrollment data	*<263>*	*<28>*	*<9>*	*<34>*	*<192>*
Consented and enrolled infants	3634	1032	1057	937	608
Enrolled outside of influenza season	*<1376>*	*<347>*	*<339>*	*<537>*	*<153>*
Consented infants during influenza season	2258	685	718	400	455
Lack complete sera pairs	*<315>*	*<47>*	*<54>*	*<93>*	*<121>*
Analytic sample	**1943**	**638**	**664**	**307**	**334**
Participation measures					
Consented to screening	97% (3919/4031)	99% (1060/1063)	95% (1080/1134)	95% (979/1031)	99% (800/803)
Consented to enrollment (among eligible)	93% (3634/3897)	97% (1032/1060)	99% (1057/1066)	96% (937/971)	76% (608/800)
Complete sera pairs	86% (1943/2258)	93% (638/685)	92% (664/718)	77% (307/400)	73% (334/455)