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The Fraction of Rhinovirus Detections Attributable to Mild and Severe Respiratory Illness in a Setting of High Human Immunodeficiency Virus Prevalence, South Africa, 2013–2015

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Abstract

Background.—The association of rhinovirus (RV) detection to illness is poorly understood.

Methods.—We enrolled case patients hospitalized with severe respiratory illness (SRI) at 2 hospitals and outpatients with influenza-like illness (ILI) and asymptomatic individuals (controls) from 2 affiliated clinics during 2013–2015. We compared the RV prevalence among ILI and SRI cases to those of controls stratified by human immunodeficiency virus (HIV) serostatus using penalized logistic regression. The attributable fraction (AF) was calculated.

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Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copy-edited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Results.—During 2013–2015, RV was detected in 17.4% (368/2120), 26.8% (979/3654), and 23.0% (1003/4360) of controls, ILI cases, and SRI cases, respectively. The RV AF (95% confidence interval) was statistically significant among children aged <5 years (ILI: 44.6% [30.7%–55.7%] and SRI: 50.3% [38.6%–59.9%]; $P < .001$) and individuals aged ≥5 years (ILI: 62.9% [54.4%–69.8%] and SRI: 51.3% [38.7%–61.3%]; $P < .001$) as well as among HIV-infected (ILI: 59.9% [45.8%–70.3%] and SRI: 39.8% [22.3%–53.3%]; $P < .001$) and HIV-uninfected (ILI: 53.6% [44.7%–61.1%] and SRI: 55.3% [45.6%–63.2%]; $P < .001$) individuals.

Conclusions.—Although RV detection was common among controls, it was also associated with a substantial proportion of clinical illness across age groups, irrespective of HIV status.

Keywords

rhinovirus; severe respiratory illness; influenza-like illness; attributable fraction

In the family Picornaviridae, the genus *Enterovirus* includes rhinoviruses (RVs) and enteroviruses [1]. RVs are among the most commonly detected viruses in patients with upper respiratory tract infection and they are considered to be associated, in most cases, with mild, self-limiting cold-like illnesses [2, 3]. However, in studies conducted in South Africa, RVs were detected in 25%–34% of upper respiratory tract specimens from patients hospitalized with severe acute respiratory illness (SARI) [4, 5].

Recent advances in the development of sensitive polymerase chain reaction (PCR) assays have considerably expanded the ability of laboratories to detect pathogens, especially viral agents. Nonetheless, establishing a clinical association between pathogen detection and illness remains challenging. Improving the understanding of the fraction of RV detection associated with mild or severe respiratory illness would provide insights for the interpretation of surveillance data, including the burden of illness associated with RV infection.

In a previous study conducted in South Africa [5], RVs were found to be significantly associated with mild and severe respiratory illness [5]; other studies could not establish this association [6–10].

Human immunodeficiency virus (HIV) infection is a known risk factor for increased severity of illness associated with the infection of several respiratory pathogens [11–14]. In the South Africa study, 26% of enrolled patients with SARI were HIV infected and the HIV prevalence was 89% among patients aged 25–44 years [5]. The significant association between RV detection and severe illness observed in this study, but not in other studies, raises the question whether the significant association found in the South Africa study was driven by the high HIV prevalence in the study population.

In this study we aimed to estimate the fraction of RV detection attributable to illness (hereafter “RV-AF”) among HIV-infected and HIV-uninfected South African patients of different age groups separately during 2013–2015. This was done among outpatients with influenza-like illness (ILI) and inpatients with severe respiratory illness (SRI). In addition,

we estimated the proportion of ILI and SRI cases attributable to RV infection after adjusting for the RV-AF.

METHODS

Severe Respiratory Illness Surveillance

We obtained samples from participants enrolled in prospective, hospital-based, SARI and severe chronic respiratory illness (SCRI) surveillance from January 2013 through December 2015 at 2 sentinel sites in the North West (Klerksdorp-Tshepong Hospital Complex, Klerksdorp) and KwaZulu Natal (Edendale Hospital, Pietermaritzburg) provinces of South Africa. We defined a case of SARI as illness in a hospitalized patient who had symptom onset within 10 days prior to admission and who met age-specific clinical inclusion criteria. A case in infants 2 days to <3 months of age included any patient with a diagnosis of suspected sepsis or physician-diagnosed acute lower respiratory tract infection, irrespective of signs and symptoms. A case in children 3 months to <5 years of age included any patient with physician-diagnosed acute lower respiratory tract infection (eg, bronchitis, bronchiolitis, and pneumonia) or pleural effusion. A case in individuals aged ≥5 years included any patient with manifestation of acute lower respiratory tract infection with recorded temperature ≥38°C or history of fever and cough. A case of SCRI was defined as illness in a hospitalized person who had symptom onset >10 days before admission and who met the age-specific clinical inclusion criteria described above. SRI cases include both SARI and SCRI cases.

Influenza-Like Illness and Asymptomatic Individuals' Surveillance

We obtained samples from participants enrolled in prospective surveillance among patients presenting with ILI and for asymptomatic persons (controls) at 2 outpatient clinics (Jouberton Clinic, North West Province, and Edendale Gateway Clinic, KwaZulu-Natal Province) located in the same catchment area as the SARI and SCRI surveillance sites from January 2013 through December 2015. We defined a case of ILI as illness in an outpatient of any age who sought medical care at one of the sentinel clinics and had a recorded temperature ≥38°C or a history of fever and cough of ≤10 days' duration.

We defined controls as persons of any age who sought medical care at one of the sentinel clinics for reasons other than fever or respiratory or gastrointestinal symptoms during the 14 days preceding the visit. Most controls visited the clinics for dental procedures, family planning, well-baby visits, voluntary HIV counseling and testing, or acute care for nonfebrile illnesses. We aimed to enroll 1 HIV-infected and 1 HIV-uninfected control every week in each clinic throughout the study period within each of the following age categories: <1 year, 1–4 years, 5–24 years, 25–44 years, 45–64 years, and ≥65 years. Controls were not followed up after enrollment.

Study Procedures

Detailed procedures for these surveillance programs have been previously described [5, 12, 15, 16]. In brief, study staff obtained informed consent and completed case report forms for all enrolled controls, inpatients, and outpatients. In addition, for inpatients, hospital records

were reviewed to assess disease progression and outcome (ie, discharge, transfer, or in-hospital death). Patients with ILI referred to hospital were excluded from the analysis.

Determination of HIV Status

HIV results were obtained from a combination of 2 sources: (1) patient clinical records when available, and (2) for consenting patients, a dried blood spot was tested at the National Institute for Communicable Diseases (NICD) of the National Health Laboratory Service, Johannesburg, South Africa. We used an HIV enzyme-linked immunosorbent assay (BioRad Genscreen HIV 1/2 V2 enzyme immunoassay [EIA] for screening and bioMérieux Vironostika HIV antigen/antibody [Ag/Ab] EIA or DiaSorin Murex HIV Ag/Ab Combination EIA for confirmation) to test samples from patients aged ≥18 months, and PCR (COBAS AmpliPrep/COBAS TaqMan HIV-1 Qualitative Test version 2.0; Roche Molecular Systems) to test samples from children aged <18 months. Limited data were available on $CD4^+$ T-cell counts on HIV-infected patients.

Sample Collection and Virus Detection

Nasopharyngeal aspirates from children aged <5 years and combined nasopharyngeal-oropharyngeal swabs from persons aged ≥5 years were collected from all participants. After collection, the specimens were placed in universal transport medium (Copan), stored at 4°C–8°C, and transported within 72 hours of collection to NICD for testing. All specimens were tested for influenza A and B viruses, respiratory syncytial virus (RSV), parainfluenza virus types 1–3, adenoviruses, human metapneumovirus, enteroviruses, and RVs, using either an in-house multiplex real-time reverse-transcription PCR assay [17] during 2013–2014 or a combination of the commercial Fast Track Diagnostics Flu/HRSV assay (Fast Track Diagnostics) and Allplex Respiratory Assay, panels 2 and 3 (Seegene) in 2015. Human bocavirus, human coronaviruses (OC43, HK1, NL63, 229E), and parainfluenza virus 4 were only tested in 2015 and were excluded from the analysis.

The platform was changed to a commercial assay because the in-house multiplex PCR was no longer available. All 10 pathogens were validated.

Statistical Analysis

We used the χ^2 or the Fisher exact test to assess association between categorical variables. In addition, we used unconditional penalized logistic regression to estimate the AF of RV-associated hospitalization and outpatient consultation by comparing the RV detection rate (observed) among ILI, SARI, and SCRI cases to those of controls. Penalized logistic regression was selected to account for separation problems (ie, no observations in one of the comparison cells) [18].

In addition, we implemented the analysis among any inpatient with SRI (ie, patients with SARI or SCRI combined). The AF was estimated from the odds ratio (OR) obtained from the logistic regression models as follows: $AF = \frac{OR-1}{OR} * 100$. Subsequently, we estimated the RV percentage positive associated with illness among patients with ILI, SARI, SCRI, and SRI ($Prev_{Illness}$) from the observed percentage positive ($Prev_{Observed}$) as follows: $Prev_{Illness} = Prev_{Observed} * AF$.

The analysis was implemented overall, and stratified by HIV serostatus within the following age categories: <1 year, 1–4 years, 5–24 years, 25–44 years, 45–64 years, and ≥65 years as well as <5 years and ≥5 years. These age groups were selected for consistency and comparability with previous studies from South Africa. All estimates were adjusted for coinfections with the other respiratory viruses investigated in this study and any underlying medical condition (treated as dichotomous variable indicating presence or absence of any evaluated condition) as they were significantly associated with the outcome. This was obtained by including covariates for any underlying medical condition and positivity for the individual viruses investigated in the study in the multivariable penalized logistic regression model.

Underlying medical conditions were asplenia, including asplenia or sickle cell anemia; chronic illness, including chronic lung, renal, liver, or cardiac disease, diabetes mellitus, and asthma; other immunocompromising conditions (excluding HIV), including organ transplant, primary immunodeficiency, immunotherapy, and malignancy; neurologic disorders; burns; obesity; malnutrition; and prematurity. Prematurity and malnutrition were included as underlying medical conditions only in the analyses implemented among children aged <1, 1–4, and <5 years.

HIV infection and age (ie, <1, 1–4, 5–24, 25–44, 45–64, ≥65) were also included as covariates in the non-HIV-stratified overall model and the models were implemented among children aged <5 years (<1 and 1–4 years) and persons aged ≥5 years (5–24, 25–44, 45–64 ≥65 years). Significant associations were considered at $P < .05$. The statistical analysis was implemented using Stata version 14.1 software (StataCorp).

Ethical Considerations

The SCRI and SARI protocol was approved by the University of the Witwatersrand Human Research Ethics Committee (HREC) and the University of KwaZulu-Natal Human Biomedical Research Ethics Committee (BREC) under protocol numbers M081042 and BF157/08, respectively. The ILI and control protocols were approved by HREC and BREC (protocol numbers M120133 and BF080/12, respectively). This surveillance was deemed nonresearch by the US Centers for Disease Control and Prevention (nonresearch determination number: 2012-6197).

RESULTS

Study Population

Over the study period, we enrolled 10 576 individuals, of whom 10 134 (95.8%) had known age and available RV and HIV results, and were thus included for further analysis. From the 10 134 study participants, 2120 (20.9%) were controls, 3654 (36.1%) had ILI, and 4360 (43.0%) had SRI. Of the 4360 patients with SRI, 2735 (62.7%) had SARI and 1625 (37.3%) had SCRI. Children aged <5 years accounted for 38.0% (806/2120) of controls, 35.5% (1297/3654) of patients with ILI, and 37.4% (1630/4360) of patients with SRI (55.6% [1520/2735] of patients with SARI and 6.7% [110/1625] of patients with SCRI).

Overall, the HIV prevalence was 41.2% (874/2120) among controls (owing to enrollment criteria for controls), 25.0% (915/3654) among patients with ILI, and 50.1% (2186/4360) among patients with SRI (37.1% [1015/2735] among patients with SARI and 72.1% [1171/1625] among patients with SCRI; $P < .001$). Across syndromes, the HIV prevalence was lowest among infants aged <1 year (1.5% [7/464] among those with ILI, 9.3% [96/1032] among those with SRI, 8.7% [84/961] among those with SARI, and 16.9% [12/71] among those with SCRI), and it was highest among patients aged 25–44 years (59.3% [581/980] among those with ILI, 90.5% [1221/1349] among those with SRI, 89.3% [509/570] among those with SARI, and 91.4% [712/779] among those with SCRI) (Supplementary Table 1).

Rhinovirus Detection and Attributable Fraction

In all age groups during the study period, RVs were detected in 23.2% (2350/10 134) of specimens from enrolled study participants, 17.4% (368/2120) among controls (Table 1), 26.8% (979/3654) among patients with ILI (Table 2), and 23.0% (1003/4360) among patients with SRI ($P < .001$; Table 3) (27.5% [751/2735] among those with SARI [Supplementary Table 2] and 15.5% [252/1625] among those with SCRI [Supplementary Table 3]).

The overall RV-AF was 54.6% (95% confidence interval [CI], 47.5%–60.8%) among patients with ILI (Table 2, Figure 1A) and 51.4% (95% CI, 43.4%–58.3%) among patients with SRI (Table 3, Figure 2A) (54.3% [95% CI, 46.3%–61.1%] among those with SARI [Supplementary Table 2] and 37.5% [95% CI, 21.5%–50.2%] among those with SCRI [Supplementary Table 3]). The RV-AF was significant among both HIV-infected and HIV-uninfected individuals with ILI (HIV infected: 59.9% [95% CI, 45.8%–70.3%] vs HIV uninfected: 53.6% [95% CI, 44.7%–61.1%]) or SRI (HIV infected: 39.8% [95% CI, 22.3%–53.3%] vs HIV uninfected: 55.3% [95% CI, 45.6%–63.2%]) (Tables 2 and 3, Figure 1B and 1C and Figure 2B and 2C). The RV-AF was also significant among HIV-infected and HIV-uninfected individuals aged <5 and ≥5 years with ILI or SRI, with the exception of HIV-infected children aged <5 years with SRI (Tables 2 and 3). Nonsignificant RV-AFs were observed in some of the other age group– and HIV-stratified analyses.

Overall, the RV AF-adjusted prevalence was 14.6% among patients with ILI (Table 2, Figure 1A) and 11.8% among patients with SRI (Table 3, Figure 2A) (14.9% among those with SARI [Supplementary Table 2] and 5.8% among those with SCRI [Supplementary Table 3]).

DISCUSSION

We assessed the association between RV detection and mild or severe respiratory illness, among HIV-infected and HIV-uninfected patients of different age groups separately. Overall, RV was significantly associated with illness across syndromes and HIV serostatus; however, this association was not significant in some age groups. The estimated detection rate attributable to illness reported in this study reflects a more accurate measure of the proportion of RV detections causing respiratory illness in both children and adults in South Africa, contrary to reporting viral detection rates alone. In our study we confirmed an overall

significant RV-AF among patients with mild or severe respiratory illness as previously described in South Africa [5].

The overall RV-AFs (ILI: 54.6%; SARI: 54.3%) found in our study were similar to those reported in a previous study conducted in South Africa (ILI: 52.0%; SARI: 46.9%), but lower compared to those of other important respiratory pathogens such as influenza viruses (ILI: 93.3%; SARI: 86.3%) and RSV (ILI: 63.1%; SARI: 83.7%) [5]. Although we found a significant RV-AF among HIV-infected and HIV-uninfected individuals across syndromes, only approximately half of the illness among RV-positive patients would be actually attributable to RV infection.

We hypothesized that the elevated HIV infection prevalence in the South African setting may have been responsible for the significant AF found in a previous South African study [5]; however, we observed that RV detection was significantly associated with both mild and severe respiratory illness also among HIV-uninfected individuals.

A study done in Thailand assessed the factors associated with RV detection [19]. Studies from Kenya, Mali, Thailand, and the United States did not find an association of RV infection with illness [6–10, 19, 20]; however, these studies had some limitations, including tests that combined RV and enterovirus detection and small sample sizes. The significant RV-AF found in this study among both HIV-infected and HIV-uninfected individuals may be due to increased power associated with the large sample size of our study compared to the above-mentioned studies.

After adjusting for the RV-AF, the proportion of illness attributable to RV (ILI: 11.8%; SARI: 14.9%) was similar to or higher than those of influenza viruses (ILI: 14.2%; SARI: 4.9%) or RSV (ILI: 5.9%; SARI: 16.7%) [5, 21]. This suggests that RV, whereas not always associated with illness when detected, may still be responsible for a substantial number of mild and severe respiratory illness cases.

Our study has limitations that warrant discussion. First, RV nucleic acids could be present during the pre- or postsyndromic phase of the infection and can be detected using PCR. In addition, we did not perform follow-up for controls after enrollment, and the development of undetected mild or severe illness for some individuals cannot be excluded. The inclusion in the control group of individuals with RV-associated symptomatic illness during the pre- or postsyndromic phase would have resulted in an underestimation of the RV-AF. Second, the role of bacterial coinfections was not investigated in this analysis. Third, the small sample size in some of the age group– and HIV-stratified analyses may have hindered our ability to reach statistical significance in some of the groups. In addition, we did not have complete $CD4^+$ count data, hindering our ability to assess the RV-AF among severely vs mildly or not immunosuppressed HIV-infected individuals. Fourth, due to low numbers, we could not assess the RV-AF among patients with very severe illness, such as intensive care unit admission or death. Last, we did not collect lower respiratory tract specimens, hindering our ability to assess a differential RV positivity proportion between lower and upper respiratory tract specimens.

In conclusion, RVs were commonly identified among asymptomatic individuals but may still be associated with a substantial proportion of mild and severe respiratory illnesses across age groups and among HIV-infected and HIV-uninfected individuals. The proportion of illness attributable to RV after adjusting for the RV-AF was similar to or higher than those of other important pathogens such as influenza viruses and RSV. This has potential implications on the prioritization of pathogens for vaccines and/or therapeutics development.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments.

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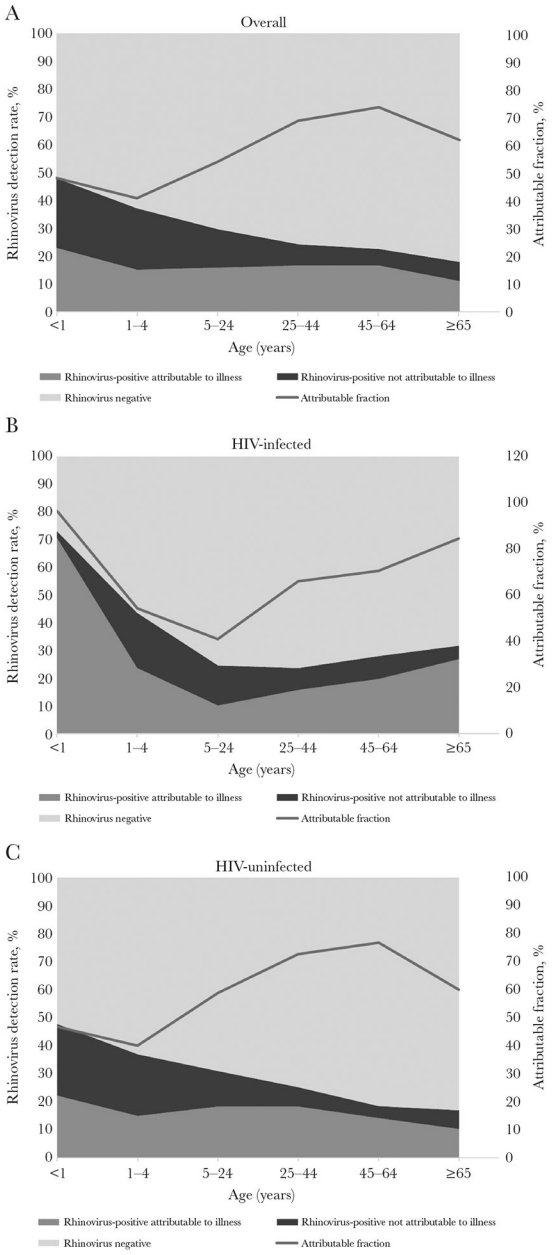

Figure 1.

Estimated rhinovirus attributable fraction and proportion of rhinovirus-positive cases attributable and not attributable to illness among outpatients with influenza- like illness, Klerksdorp and Pietermaritzburg, South Africa, January 2013–December 2015.

Abbreviation: HIV, human immunodeficiency virus.

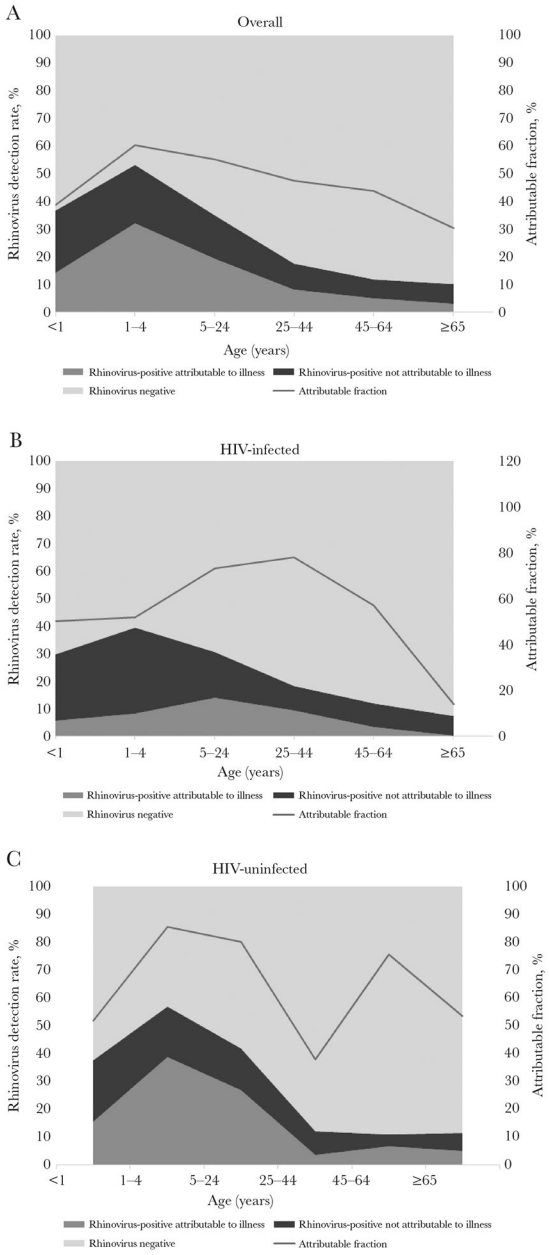

Figure 2.

Estimated rhinovirus attributable fraction and proportion of rhinovirus-positive cases attributable and not attributable to illness among patients hospitalized with severe respiratory illness, Klerksdorp and Pietermaritzburg, South Africa, January 2013–December 2015.

Abbreviation: HIV, human immunodeficiency virus.

Table 1.

Asymptomatic Individuals Positive for Rhinovirus Infection, Klerksdorp and Pietermaritzburg, South Africa, January 2013–December 2015

Age, y	All, Positive/Total, No. (%)	HIV-Infected, Positive/Total, No. (%)	HIV-Uninfected, Positive/Total, No. (%)
<1	98/339 (28.9)	7/31 (22.6)	91/308 (29.5)
1–4	121/467 (25.9)	53/205 (25.9)	68/262 (26.0)
5–24	94/592 (15.9)	43/280 (15.4)	51/312 (16.3)
25–44	27/310 (8.7)	17/189 (9.0)	10/121 (8.3)
45–64	18/280 (6.4)	12/141 (8.5)	6/139 (4.3)
>65	10/132 (7.6)	3/28 (10.7)	7/104 (6.7)
<5	219/806 (27.2)	60/236 (25.4)	159/570 (27.9)
≥5	149/1314 (11.3)	75/638 (11.8)	74/676 (10.9)
All	368/2120 (17.4)	135/874 (15.4)	233/1246 (18.7)

Abbreviation: HIV, human immunodeficiency virus.

Table 2.

Rhinovirus Detection and Attributable Fraction Among Outpatients With Influenza-Like Illness by Human Immunodeficiency Virus Infection Status, Klerksdorp and Pietermaritzburg, South Africa, January 2013–December 2015

	All Outpatients With Influenza-Like Illness			HIV-Infected			HIV-Uninfected		
	Attributable Fraction	Observed Detection Rate	Adjusted Detection Rate	Attributable Fraction	Observed Detection Rate	Adjusted Detection Rate	Attributable Fraction	Observed Detection Rate	Adjusted Detection Rate
Age, y[a]	% (95% CI)	no./No. (%)	%	% (95% CI)	no./No. (%)	%	% (95% CI)	no./No. (%)	%
<1	**48.1 (28.6–62.3)**	181/464 (39.0)	18.8	96.5 (0–99.9)	3/7 (42.9)	41.4	**46.7 (26.4–61.5)**	178/457 (38.9)	18.2
1–4	**40.8 (18.9–56.8)**	269/833 (32.3)	13.2	54.3 (0–86.0)	6/17 (35.3)	19.2	**40.1 (17.0–56.8)**	263/816 (32.2)	12.9
5–24	**53.9 (38.8–65.2)**	248/970 (25.6)	13.8	**40.9 (.9–64.8)**	34/152 (22.4)	9.2	**58.8 (41.9–70.8)**	214/818 (26.2)	15.4
25–44	**68.7 (52.2–79.5)**	204/980 (20.8)	14.3	**66.0 (41.8–80.1)**	119/581 (20.5)	13.5	**72.6 (46.0–86.2)**	85/399 (21.3)	15.5
45–64	**73.5 (54.2–84.6)**	68/351 (19.4)	14.3	**70.5 (41.0–85.2)**	36/154 (23.4)	16.5	**76.7 (44.0–90.3)**	32/197 (16.2)	12.4
>65	61.7 (0–85.6)	9/56 (16.1)	9.9	84.4 (0–98.8)	1/4 (25)	21.1	59.9 (0–86.0)	8/52 (15.4)	9.2
<5	**44.6 (30.7–55.7)**	450/1297 (34.7)	15.5	**68.6 (10.6–88.98)**	9/24 (375)	25.7	**43.6 (29.1–55.2)**	441/1273 (34.6)	15.1
≥5	**62.9 (54.4–69.8)**	529/2357 (22.4)	14.1	**59.5 (44.5–70.49)**	190/891 (21.3)	12.7	**64.4 (53.0–73.0)**	339/1466 (23.1)	14.9
All	**54.6 (47.5–60.8)**	979/3654 (26.8)	14.6	**59.9 (45.8–70.3)**	199/915 (21.7)	13.1	**53.6 (44.7–61.1)**	780/2739 (28.5)	15.3

Significant values are indicated in bold. Age group and HIV infection were also included as predictors in nonstratified models.

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus.

[a]The overall rhinovirus attributable fraction was obtained from models adjusted for any underlying medical conditions and for other respiratory viruses investigated in this study.

Table 3.

Rhinoviruses Detection and Rhinoviruses Attributable Fraction Among Patients Hospitalized With Severe Respiratory Illness by Human Immunodeficiency Virus Infection Status, Klerksdorp and Pietermaritzburg, South Africa, January 2013–December 2015

	All Inpatients With Severe Respiratory Illness			HIV-Infected			HIV-Uninfected		
	Attributable Fraction	Observed Detection Rate	Adjusted Detection Rate	Attributable Fraction	Observed Detection Rate	Adjusted Detection Rate	Attributable Fraction	Observed Detection Rate	Adjusted Detection Rate
Age, y[a]	% (95% CI)	no./No. (%)	%	% (95% CI)	no./No. (%)	%	% (95% CI)	no./No. (%)	%
<1	**38.8 (176–54.5)**	332/1032 (32.2)	12.5	18.6 (0–68.8)	27/96 (28.1)	5.2	**41.5 (20.0–573)**	305/936 (32.6)	13.5
1–4	**60.2 (45.8–70.7)**	241/598 (40.3)	24.3	20.3 (0–58.0)	30/82 (36.6)	7.4	**68.4 (54.6–779)**	211/516 (40.9)	28
5–24	**55.2 (372–68.0)**	96/328 (29.3)	16.2	**45.5 (13.5–65.6)**	53/198 (26.8)	12.2	**64.0 (41.3–78.0)**	43/130 (33.1)	21.2
25–44	**474 (18.8–65.9)**	219/1349 (16.2)	7.7	**51.1 (18.1–70.8)**	204/1221 (16.7)	8.5	30.4 (0–69.9)	15/128 (11.7)	3.6
45–64	**43.8 (5.0–66.7)**	92/824 (11.2)	4.9	26.5 (0–61.2)	62/535 (11.6)	3.1	**60.4 (5.0–83.5)**	30/289 (10.4)	6.3
>65	30.5 (0–68.0)	23/229 (10.0)	3.1	−23.7 (0–71.7)	4/54 (74)	0	42.7 (0–76.7)	19/175 (10.9)	4.7
<5	**50.3 (38.6–59.9)**	573/1630 (35.2)	15.7	21.2 (0–53.8)	57/178 (32.0)	6.8	**56.0 (44.3–65.3)**	516/1452 (35.5)	19.9
≥5	**51.3 (38.7–61.3)**	430/2730 (15.8)	8.1	**44.8 (25.6–59.1)**	323/2008 (16.1)	7.2	**57.9 (39.9–70.5)**	107/722 (14.8)	8.6
All	**51.4 (43.4–58.3)**	1003/4360 (23.0)	11.8	**39.8 (22.3–53.3)**	380/2186 (174)	6.9	**55.3 (45.6–63.2)**	623/2174 (28.7)	1.9

Significant values are indicated in bold. Age group and HIV infection were also included as predictors in nonstratified models.

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus.

[a]The overall rhinovirus attributable fraction was obtained from models adjusted for any underlying medical conditions and for other respiratory viruses investigated in this study.