Supplementary Material

TITLE: Diagnosis of Respiratory Syncytial Virus in Adults substantially increases when adding sputum, saliva, and serology testing to nasopharyngeal swab RT-PCR

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1. Norton Infectious Diseases Institute RSV in Adults Study Group

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2. Clinical Studies Coordinating Center (CSCP)

Norton Infectious Diseases Institute (NIDI) was established in June 2020 to facilitate collaboration between professionals across multiple specialties of infectious diseases. NIDI is structured into five centers: 1) Clinical Research Center; 2) Global Health Center; 3) Education and Training Center; 4) Public Health Center; 5) Medical Practice. The organizational structure of NIDI is displayed in **e-Figure 1**.

Figure E1: Norton Infectious Diseases Institute Clinical Research Center Structure

The NIDI Clinical Research Center (CRC) provides support for all clinical research-related activities within the institute. The mission of the CRC is to maintain integrity among all aspects of clinical research, while providing education and training for individuals, regardless of background and skill-level, interested in clinical research. Nested within the NIDI CRC, the Clinical Studies Coordinating Program (CSCP) enlists experienced professionals for the proper coordination of multicenter clinical studies. The CSCP strives to produce high-quality clinical research by providing support and oversight during the entire research process. The CSCP maintains consistency across all NIDI study sites by ensuring adherence to standard procedures outlined in the protocol, appropriate interaction of study personnel with facility staff and patients, and that all data is validated, securely stored, and properly analyzed. The individual units and lead members of the CSCP are depicted in Figure E2.

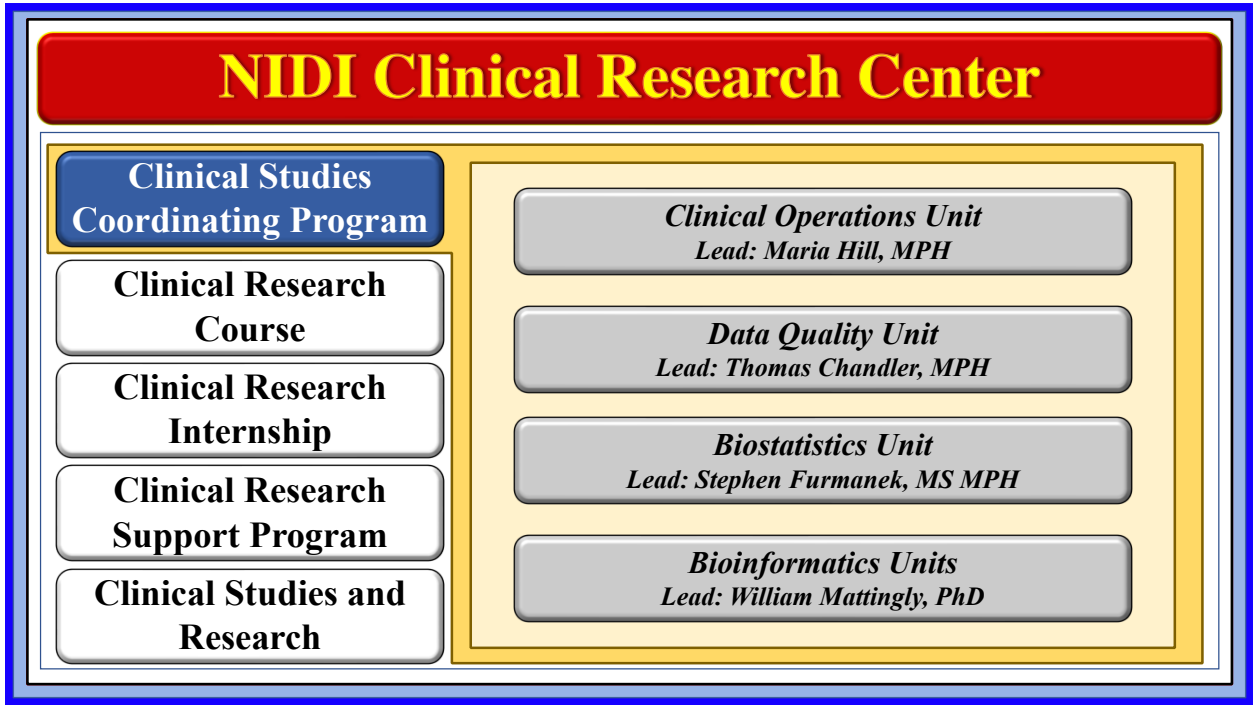

Figure E2: Organizational structure of the Norton Infectious Diseases Institute (NIDI) Clinical Studies Coordinating Program (CSCP).

3. Participating Norton Healthcare Facilities

Patients hospitalized at any of the four acute-care Norton hospitals were screened for study inclusion. Information regarding each participating facility is as follows:

A. Norton Audubon Hospital

Norton Audubon Hospital is a 432-bed facility offering a full range of highly specialized medical and surgical services, including an internationally recognized heart institute and Chest Pain Center.

B. Norton Women and Children's Hospital

In addition to being the primary provider of obstetrical services in Kentucky, Norton Women & Children's Hospital is a 373-bed facility offering a full range of diagnostic, therapeutic, emergency and surgical services for men, women and children.

C. Norton Hospital

Located in downtown Louisville, Norton Hospital is a 605-bed facility that focuses on specialty surgical services and advanced diagnostics. Norton Hospital is nationally recognized for their oncological services and is the preferred facility for birthing high-risk pregnancies.

D. Norton Brownsboro Hospital

Norton Brownsboro Hospital is a 197-bed facility offering a full range of outpatient, inpatient and intensive care services. This facility is nationally recognized for their high-level treatments of cerebrovascular events and neurosurgical conditions.

4. Screening Process and Criteria

Daily reports of newly admitted hospitalized patients aged 40 and older were screened for participation in the study using the following signs and symptoms of acute respiratory illness: a chief complaint of cough, shortness of breath, shortness of air, nasal congestion, rhinorrhea, sore throat, hoarseness, cough, sputum production, wheezing, hypoxemia; or using admitting diagnosis of suggestive of ARI (e.g. pneumonia, bronchitis, or upper respiratory infection) or exacerbation of underlying cardiopulmonary disease involving acute respiratory symptoms (e.g. acute exacerbation of COPD, acute decompensation of heart failure, acute exacerbation of asthma). Patients with at least one positive pre-screening criterion were screened for full inclusion criteria as described in the full body of the manuscript. Screening was conducted in the mornings and afternoons to attempt to catch all newly admitted patients at study hospitals.

5. Data Integrity and Quality Management

Clinical research coordinators were trained using standard operating procedures and simulations to ensure adequate sample collection and consistency in the consenting and enrollment process. Clinical research coordinators were also trained for data collection to ensure consistent data capture.

Clinical research coordinators were responsible for enrolling study subjects, collecting biological specimen, and recording available clinical data from the patient's medical record at the time of enrollment on a paper case report form (CRF). Study data was recorded and stored on a secure, web-based database application hosted by Norton Healthcare.

Data quality issues identified on the paper CRF were fixed prior to recording data in the electronic database, and then locked and stored in a secure location. At the time of data entry, several data quality checks were built-in to the study date base to limit out-of-range values and inaccurate data. Weekly quality meetings were held to address any quality issues and queries. After all data queries were resolved, each record case was accepted into the database for analysis.

6. Supplemental Tables

E-Table 1. Patient Characteristics for the Study Population

Variable	**Enrolled Patients n=1766**
Age, (median [IQR])	65 [56, 74]
Male sex, n (%)	797 (45)
Race/Ethnicity	
White race, n (%)	1231 (70)
Black or African American race, n (%)	443 (25)
Asian race, n (%)	8 (1)
Other race, n (%)	84 (5)
Hispanic ethnicity, n (%)	59 (3)
Residence in 2 weeks prior to admission, n (%)	
Home	1669 (95)
Rehabilitation center	10 (1)
Skilled nursing facility	39 (2)
Other residence	38 (2)
Underlying Comorbidities*	
Obesity (BMI > 40), n (%)	260 (15)
Diabetes mellitus, n (%)	688 (39)
Coronary artery disease, n (%)	564 (32)
Congestive heart failure, n (%)	587 (33)
Chronic obstructive pulmonary disease, n (%)	675 (38)
Asthma, n (%)	334 (19)
Other chronic lung disease, n (%)	125 (7)
Chronic kidney disease, n (%)	386 (22)
Neurologic and Neurodevelopment conditions, n (%)	260 (15)

Immunocompromised**, n (%)	494 (28)
No comorbidity***, n (%)	118 (7)

*Comorbidities are not mutually exclusive, and patients may have more than one comorbidity. Comorbidities collected but not shown are blood disorders, stroke, chronic liver disease, other chronic heart disease, and current pregnancy.

Immunocompromised includes persons with autoimmune disorders, active immunosuppressant drug therapy, immunodeficiency, HIV, AIDS, Cancer, solid tumor or hematologic malignancy, or organ transplant. * No comorbidity was defined as a participant being non-immunocompromised with no comorbidities depicted in the table, and no blood disorder, stroke, chronic liver disease, other chronic heart disease, or current pregnancy.

E-Table 2. Characteristics of RSV patients identified by NP swab compared with RSV patients identified by other specimen types only

	All RSV+ Patients (by any specimen type)		NP Swab Test Positive*		NP Swab Negative & Saliva/Sputum Positive		NP Swab Test Negative & Serum Test Positive		NP Swab Test Negative & Any other test Positive	
	N	%	N	%	N	%	N	%	N	%
Overall	109	100.0	56	100.0	37	100.0	16	100.0	53	100.0
Age in Years										
Median(Q1, Q3)	64.0	57.0, 74.0	68.0	57.5, 75.0	61.0	55.0, 75.0	63.5	60.5, 69.5	62.0	55.0, 70.0
40-64	56	51.4	24	42.9	24	64.9	8	50.0	32	60.4
≥65	53	48.6	32	57.1	13	35.1	8	50.0	21	39.6
Time from symptom onset to swab collection in days**										
Median(Q1, Q3)	4.0	2.0, 7.0	4.0	2.0, 6.0	3.0	2.0, 7.0	6.0	3.0, 8.5	4.0	2.0, 7.0
0 days (on the same day)	4	3.7	2	3.6	2	5.4	0	0.0	2	3.8
1-2 days	31	28.4	14	25.0	13	35.1	4	25.0	17	32.1
3-4 days	28	25.7	18	32.1	9	24.3	1	6.3	10	18.9
≥ 5 days	46	42.2	22	39.3	13	35.1	11	68.8	24	45.3
Signs and Symptoms										
Dyspnea (shortness of breath/air)	99	90.8	50	89.3	35	94.6	14	87.5	49	92.5
Cough	75	68.8	46	82.1	22	59.5	7	43.8	29	54.7
Sputum production	66	60.6	39	69.6	22	59.5	5	31.3	27	50.9
Wheezing	40	36.7	28	50.0	10	27.0	2	12.5	12	22.6
Nasal congestion	21	19.3	13	23.2	7	18.9	1	6.3	8	15.1
Hypoxemia (low blood oxygen)	19	17.4	14	25.0	3	8.1	2	12.5	5	9.4
Rhinorrhea (Runny nose)	14	12.8	7	12.5	7	18.9	0	0.0	7	13.2
Sore throat	8	7.3	5	8.9	3	8.1	0	0.0	3	5.7
Hoarseness	4	3.7	3	5.4	1	2.7	0	0.0	1	1.9
Final Clinical Diagnosis										
Other respiratory/pulmonary disease	37	33.9	20	35.7	11	29.7	6	37.5	17	32.1

Acute exacerbation of COPD	19	17.4	11	19.6	5	13.5	3	18.8	8	15.1
Community-acquired pneumonia (CAP)	14	12.8	7	12.5	5	13.5	2	12.5	7	13.2
Other cardiac disease	11	10.1	4	7.1	7	18.9	0	0.0	7	13.2
Other non-respiratory/pulmonary disease	10	9.2	4	7.1	3	8.1	3	18.8	6	11.3
Acute bronchitis	9	8.3	7	12.5	2	5.4	0	0.0	2	3.8
Acute decompensation of heart failure	9	8.3	3	5.4	4	10.8	2	12.5	6	11.3
Immunocompromised	33	30.3	13	23.2	14	37.8	6	37.5	20	37.7

* NP swab test positive may include patients who are also saliva or sputum or serology test positive.
** Some patients may have symptom onset date missing.
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