

Site Training

MARC-35:
Prospective Cohort Study
of Severe Bronchiolitis and
Risk of Recurrent Wheezing



Outline of Presentation

1. Overview
2. Enrollment
3. Specimen Collection
4. Follow-up by Sites

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Aims

1. To examine the association between:
 - (a) the infectious etiology of a child's severe bronchiolitis, and (b) the severity of this illness, and the subsequent development of recurrent wheezing by age 3 years (*primary aim*)
 - the level of serum 25-hydroxyvitamin D (25[OH]D) during severe bronchiolitis and the subsequent development of recurrent wheezing by age 3 years

Aims (continued)



2. To combine these clinical and laboratory data to derive the wheezing index (WIND), a new clinical index that will identify children at higher risk of developing recurrent wheezing by age 3 years
3. To create a biorepository that will permit future testing of novel mechanistic hypotheses

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MARC-35 Sites

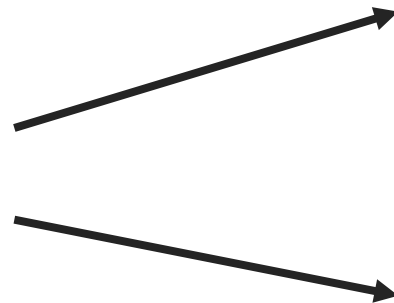


Site Enrollment Goal



November 1 until April 30

30 subjects



~ 24 subjects
from medical ward

~ 6 subjects from
ICU

Site Enrollment Goal (continued)



- Nov 1 – April 30 → ICU patients
- Dec 1 – Feb 28 → ward patients
- Sites may
 - Enroll ward patients in months other than December – February
 - Enroll >30 patients

Site Enrollment Goal (continued)



| | Year 1 (n=9 sites) | Year 2 (n=17 sites) | Year 3 (n=6 sites) | Total |
|----------------|-----------------------|------------------------|-----------------------|-------|
| Fully Enrolled | 149 | 662 | 230 | 1041 |

Inclusion Criteria

- Age <1 year
- Admitted to hospital with attending physician diagnosis of bronchiolitis (AAP definition)
- Informed consent given ≤ 24 hours of admission to hospital or ICU
- Parent speaks English or Spanish

Inclusion Criteria (continued)



- Permanent address, phone, email, alternate contact information, and primary care provider for next year
- Some exceptions to “permanent” info:
 - Legal guardians who are college students
 - Military personnel NOT expecting to be deployed in next 12 months
 - Families who plan to move locally in next 12 months

Exclusion Criteria

- Already enrolled in the current study
- Parent does not agree to collection of specimens or future use of specimens
- Transferred >48 hours after original admission
- Time since child transferred to a participating site hospital >24 hours
- Already meets primary endpoint (rec. wheeze)
- Known heart-lung disease, immunodeficiency, immunosuppression or gestational age <32 wk
- Not English or Spanish speaking

Identify Potential Participants



- Develop system to monitor admissions
- Confirm physician diagnosis of bronchiolitis with medical team
- Enrollment is not necessarily consecutive, but high capture will help site to meet goal:
 - Consent obtained ≤ 24 h of admission
 - Interview & NPA collection immediately after

Screening Form

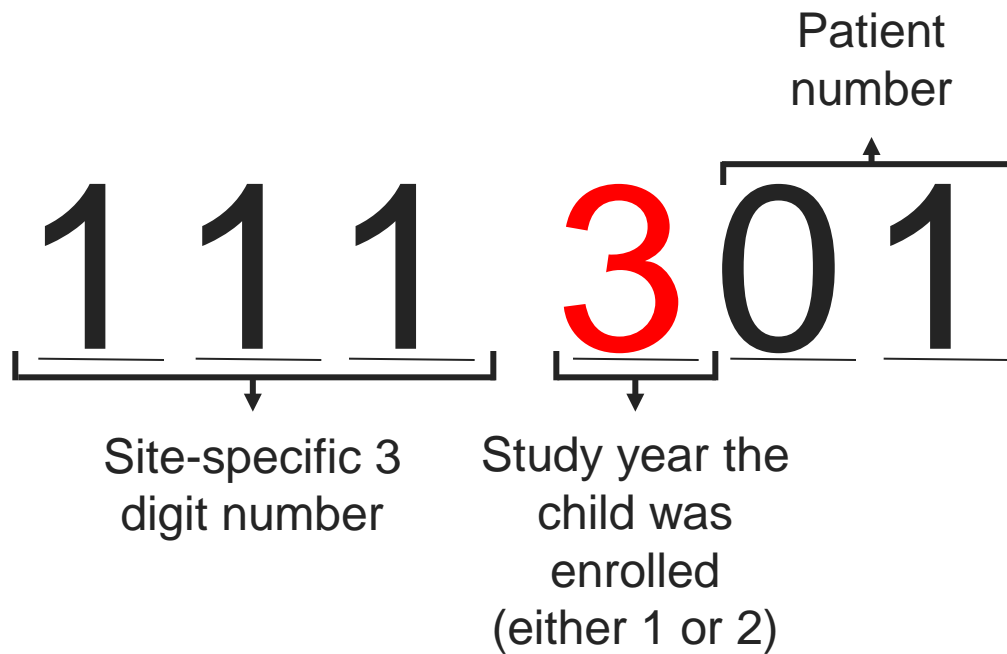
Fill out for every infant (age <1y) admitted to hospital with bronchiolitis during designated months of screening

- ICU: November – April
- Ward:
 - December – February
 - Any ward patients approached November, March, and April (i.e., outside the designated 3-month ward recruitment period)

Study ID

- After Consent Form signed → answer the last question on Screening Form, which confirms enrollment
- Assign each enrolled participant a unique Study ID #
- Record the study ID # on Screening Form

Study ID# (continued)



Intake Form



In order to minimize “unknown” as a participant response, please do not read “UKN” as an option to participant

Intake Form – Ethnicity / Race



- Self-identified
- If a participant says that he/she is of Latino/Hispanic origin and their race is "other" ask follow-up questions to help determine race (eg, white Hispanic)

Intake Form – Episode

“Episodic” healthcare utilization reporting
(excludes visits earlier in same question)

Hospital visits

| | |
|--|---|
| <p>a. How many times was [child] admitted to the hospital for this breathing problem? <i>For each admission:</i></p> <p>1. Hospital name/location: _____</p> <p>2. Admit date _____</p> <p>3. Was [child] seen in doctor’s office, clinic or ED before hospital admission?</p> <p>1. office/clinic only 2. ED only 3. Office/clinic → ED 4. No (e.g., Transfer from other hospital)</p> <p> If 1 or 3, then Office/Clinic Name/ Location: _____</p> <p> If 2 or 3 then ED Name/ Location: _____</p> <p>4. Was [child] admitted to ICU at any time during this hospitalization? Y N</p> <p>5. Was [child] intubated? Y N</p> | <p>_____</p> <p>write</p> <p>__ / __ / __</p> <p>_____</p> <p>_____</p> <p>write</p> <p>write</p> <p>_____</p> <p>_____</p> |
|--|---|

ER Visits

| | |
|--|--|
| <p>(NOTE TO INTERVIEWER: If any ER visits were already recorded, read the following statement. Otherwise skip directly to the question.)</p> <p>Not counting any ER visits we may have just discussed... (ER visit → hospital admission)</p> <p>a. How many times did [child] have an ER visit for this breathing problem? <i>For each ER visit:</i></p> <p>1. Hospital name/location: _____</p> <p>2. Visit date _____</p> <p>3. Was [child] seen in doctor’s office or clinic before ED visit? Y N</p> <p> If yes, then Doctor/ Clinic Name/ Location: _____</p> | <p>_____</p> <p>write</p> <p>__ / __ / __</p> <p>_____</p> <p>_____</p> <p>write</p> |
|--|--|



Intake Form – Site Use Only



- Withdrawal of **consent** before completion of form
 - If yes → briefly explain
- Enrolled, but later determined to be ineligible (eg, non-working phone number)
 - If yes → briefly explain and clarify which Screening Form question(s) were answered incorrectly

Chart Review Reminders

- Avoid inferences or assumptions
- Choose “not documented” when something is not written in the medical record. Lack of documentation does not imply adequate or normal – or inadequate or abnormal.
- Understand what viruses are included in your hospital’s respiratory panel
- Double-check your entries to avoid transcription errors

Chart Review Reminders

- Be aware of admission and discharge dates and times
- Pay attention to the timing of specific question (eg, pre-admission vs. admission values)
- “Initial vitals” on Intake Chart Review:
 - First vitals from clinic (if clinic → hospital)
 - First vitals from ED (if ED → hospital)
 - First vitals from ED (if clinic → ED → hospital)
- Inpatient Chart Review: Important – Discharge date **MUST** be filled out as soon as patient is discharged

QA Chart Review

- EMNet received index hospitalization records for the first 3 study participants at each site
- EMNet answered 20+ questions from Intake Chart Review and Inpatient Form based on then charts available to us
- We then assessed congruence between site's response and our review

Chart Review: Problematic Questions



| Question | Answer Choices |
|--|---|
| By the conclusion of pre-admission visit (or day of transfer) patient had... | <ol style="list-style-type: none">1. Adequate oral intake2. Inadequate oral intake3. Not documented |
| Air entry (Initial vitals) | <ol style="list-style-type: none">1. Normal2. Abnormal3. Not documented |
| Presence of wheezing? (Pre-admission) | <ol style="list-style-type: none">1. Yes2. No3. Not documented |

Remember: If something is not written in the medical record, choose not documented. Avoid making assumptions or inferences!

Chart Review: Problematic Questions



| Question | Answer Choices |
|---|----------------|
| Inhaled bronchodilator in first 24 hours of admission? | Yes/No |
| CBC with differential? (during inpatient hospitalization) | Yes/No |

Remember: Time is an important component of many questions. Before starting any chart review, it's critical to know the dates/times of pre-admission, admission, and discharge. Some questions may be similar but refer to different points in the healthcare encounter.

QA: Telephone Interview

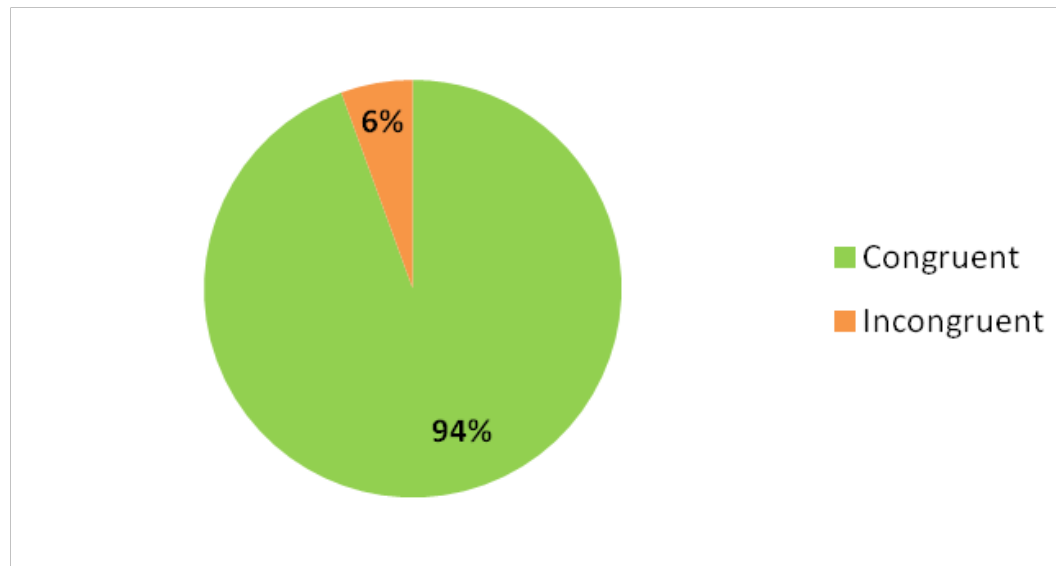
- Participants randomly selected from sites
- Approximately 10% sample
- Re-administered 5 questions from Intake Form during the 3-week interview
 - How much did [*child*] weigh when he/she was born?
 - Does [*child*] have a history of eczema also known as atopic dermatitis? By eczema we mean an itchy scaly rash that comes and goes.
 - How would you describe the kind of building where [*child*] lives?
 - Has [*child*] ever attended daycare outside the home?
 - Has anyone who has EVER lived with, taken care of, or seen [*child*] on a regular basis, ever smoked near [*child*]?

QA: Telephone Interview



Across all sites:

4.72 out of 5 responses matched (94% congruent)



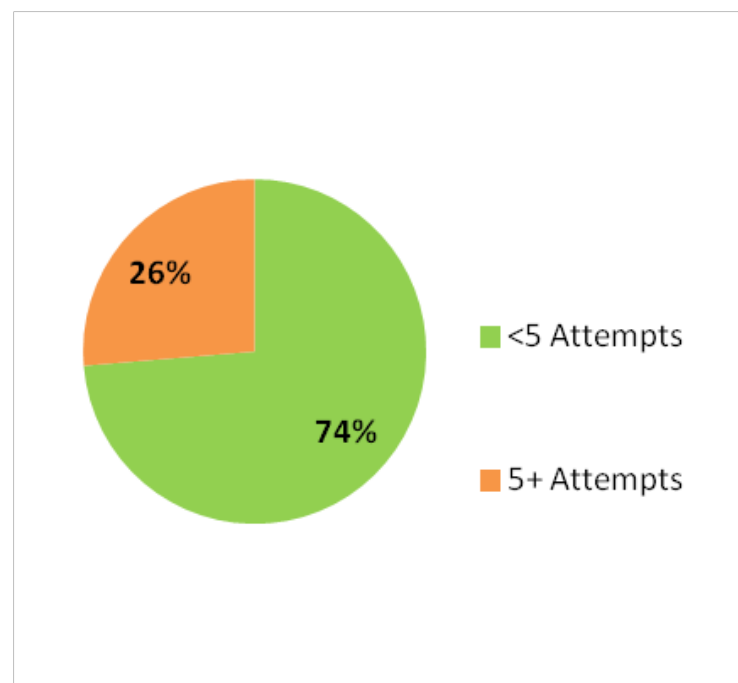
Contact Form

- Extremely important for long term follow-up to collect as much information as possible
- Required:
 - Phone, mailing address, email
 - PCP name and contact info
 - 1 alternate contact
- Note that email and alternate contact info can be given as late as 1-week phone call

Follow-up Call Attempts

Reached in <5 attempts:

- 6-month follow-up call: 79%
- 12-month follow-up call: 71%
- 18-month follow-up call: 67%
- 24-month follow-up call: 66%
- **Total follow-up calls: 74%**



Contact Form – SSN, Testing



- Social Security Number (SSN)
 - Required for payment
 - Not required if parent willing to participate without remuneration
 - Reassure parent that SSN will remain strictly confidential

- Indicate if parent wants test results (ie, NPA virology & 25[OH]D) sent to PCP

Maternal Pregnancy & Nutrition



- Two versions of form:
 1. For biological mother → asks about “you”
 2. For non-biological mother (eg, adoptive parent), father, grandparent, etc. → asks about “biological mother”

- If possible, we want response from the biological mother

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Specimen Enrollment Checklist



- After collecting specimens, a participant:
 1. Is fully enrolled ...
 2. Did not fulfill enrollment requirements ... or
 3. Withdrew consent before end of enrollment

- Status is reflective of enrollment *immediately after specimen collection*

Specimen Collection – Overview



Enrollment in the study requires the collection of:

1. Blood
2. Nasopharyngeal aspirate (NPA) specimen
3. Nasal swab
4. Stool

Blood Collection

- Collect blood at anytime, but ideally within 24h
- Likely will be the enrollment limiting step
- Pain minimizing techniques may be used
- Minimum blood volume = 5 mL
 - Use of discarded blood from red top tubes is allowable
 - <5 mL requires a waiver; contact Ashley
- Use the provided red top tubes
- Label the tube with pre-printed study label

Blood Collection (continued)

- Blood collected for CBC
 - Should be drawn into **purple top tube** prior to collection of other blood
- Blood for research purposes (25OHD, IgE, etc.)
 - Should be drawn into **red top tubes**
 - May use discarded blood also in **red top tubes** to meet minimum volume; if yes, must spin.
- Discarded blood not in red top tubes
 - Should be transferred to cryotubes for -80 freezer storage and shipped with blood from red top tubes

Blood Processing

- Take blood sample to your lab
- Centrifuge the red top tube blood to separate serum (clear fluid on top) from remaining contents (red pellet on bottom)
- For specific details on Blood Serum and Pellet procedures please see Appendix E2

Blood Storage

Label and then store upright in 2 separate tubes at -70°C or -80°C :

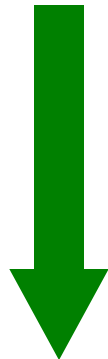
- Serum (clear top tube)
- Remaining contents - the pellet (blue top tube)

Where to ship *serum and any discarded blood* if:



- Fully enrolled (Chronic & Acute cohort)
- Found ineligible *
- Did not fulfill enrollment requirements *
- Withdrew after index hospitalization *

Withdrew during index hospitalization



MGH

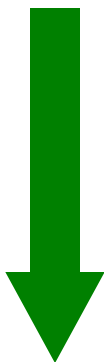


**Do NOT ship –
destroy specimens!**

* Unless otherwise specified by your site-specific consent form

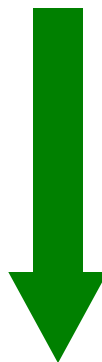
Where to ship *pellet* if:

Fully enrolled
(Chronic & Acute
cohort) AND
consented to
genetic portion of
study



University of Arizona

- Fully enrolled (Chronic & Acute cohort) but did NOT consent to genetic portion of study
- Found ineligible *
- Did not fulfill enrollment requirements *
- Withdrew after index hospitalization *



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Withdrew during
index
hospitalization



**Do NOT ship –
destroy specimens!**

* Unless otherwise specified by your site-specific consent form

Serum and Pellet Shipping



- Serum and pellet will be shipped once (May)
- Specimens should be shipped overnight
- Only personnel with IATA certification may package and ship blood
- Only ship specimens Mon, Tue, or Wed

NPA Collection



- We will send you individually packaged NPA collection kits (all required contents included)
- Must be done within 24 hours of admission
- Visit website (www.emnet-usa.org) for complete collection and handling instructions, as well as the NPA collection video
- Label NPA with pre-printed study label

NPA Collection (continued)

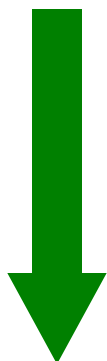


Reminders:

- All NPA specimens will be collected through the nose, even for children intubated or on CPAP
- Volumes should be standard across participants
 - Ideal is 6-8 ml, though 4-6 ml is common
 - Consistent volumes at site are important
 - We want to identify and quantify the virus

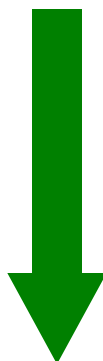
Where to ship *NPA* if:

Fully enrolled
(Chronic & Acute cohort)



Baylor

- Found ineligible *
- Did not fulfill enrollment requirements *
- Withdrew after index hospitalization *



MGH

Withdrew during
index hospitalization



**Do NOT ship –
destroy specimens!**

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NPA Shipping

- NPAs shipped overnight in May
- Only personnel with IATA certification may package and ship NPA. Packaging must include Biological Substance, Category B labels
- Only ship on Mon, Tue, or Wed

Index Nasal Swab

- Purpose:
 - To compare to the “gold standard” NPA results
 - To compare to later nasal swab collections performed by parent
 - To teach parent technique
- *Ideally*, index nasal swab should be done
 - within 24 hours of admission
 - 2+ hours after NPA

Index Swab Storage & Shipment



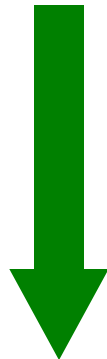
- Nasal swab specimens will NOT be stored on-site
- They should be shipped to MGH as soon as they are collected
- Swab shipments do NOT require IATA certification and the boxes do not need biohazard labels

Where to ship *index nasal swab* if:



- Fully enrolled (Chronic & Acute cohort)
- Found ineligible*
- Did not fulfill enrollment requirements*
- Withdrew after index hospitalization*

Withdrew during
index hospitalization



MGH



**Do NOT ship –
destroy specimens!**

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Overview: Microbiome

- After birth, infants rapidly colonized with trillions of commensal microbes
 - Microbiota: infant's collection of microorganisms
 - Microbiome: collective genomes of microorganisms
 - Exposed surfaces: GI, nose/airway, skin, vagina

- Factors thought to influence composition
 - Mode of delivery, breastfeeding/diet, medications (antibiotics, acid blockers), maternal microbiome, Vitamin D status, animal exposure, etc.
 - Relatively stable, adult-like composition by age 1

Microbiome: Health & Disease



- Normal, diverse infant microbiome may promote healthy child development
 - Aids digestion, regulates energy extraction
 - Promotes normal immune system development
 - Prevents colonization/overgrowth of pathogens

- Alterations (dysbiosis) may contribute to disease
 - Differences between gut flora of children in developing vs. industrialized nations
 - Evidence mounting: role in obesity, IBD, necrotizing enterocolitis, atopy (asthma, eczema, allergic rhinitis)

Microbiome: Atopy & Stool



- Why atopy? In germ-free mice, microbiota:
 - Drives T_H1 cell differentiation, which corrects T_H2 skewing present at birth
 - Promotes Treg cell differentiation, immune tolerance
- Why stool?
 - Gut has largest microbe collection (~10-100 trillion)
 - Largest stimulus of immune system development
 - Noninvasive to collect
 - Compare bronchiolitis gut microbiome to “healthy”
 - Later, compare infant gut microbiome of recurrent wheezers to non-recurrent wheezers

Specimen Collection – Stool



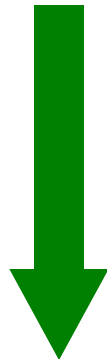
- ¼ teaspoon collected from dirty diaper during hospitalization
- Diaper needs to be refrigerated until stool moved to storage tube; then freeze tube within 24 hours at -80°
- Protocol to be refined at Boston Children's
- Anticipated collection start date = Dec 1

Where to ship *stool* if:



- Fully enrolled (Chronic & Acute cohort)
- Found ineligible *
- Did not fulfill enrollment requirements *
- Withdrew after index hospitalization *

Withdrew during
index hospitalization



MGH



**Do NOT ship –
destroy specimens!**

* Unless otherwise specified by your site-specific consent form

Labels

- Make sure the Study ID # matches the # on the labels
- You will need 10 labels
- EMNet will send labels to sites pre-printed with study ID

| Label use | Label amount |
|-------------------------------------|--------------|
| Consent forms | WRITE |
| Maternal nutrition & pregnancy form | 1 |
| NPA | 1 |
| Index swab | 1 |
| Blood draw tube | 1 |
| Serum tube | 1 |
| Pellet tube | 1 |
| ARI swab kit vial | 1 |
| ARI swab kit form | 1 |
| Clearance kit vial | 1 |
| Clearance kit form | 1 |
| TOTAL | 10 |

Before Discharge

- Site personnel will need to be up-to-date about discharge planning

- Visit patient before discharge
 - To reaffirm personal connection
 - Schedule a good time for 1-week post discharge follow-up call
 - Hand-out nasal swab kits and emphasize importance of completing nasal swabs

Before Discharge - Nasal Swab Kit



- Prepare 2 swab kits to give parent:
 - Clearance (3 weeks post-admission)
 - ARI (for future breathing problem)

- Each kit should contain all materials necessary for specimen collection:
 - 1 Introductory Letter*
 - 1 “When to use this kit” instructions*
 - 1 Survey*
 - 1 Nasal Swab Collection instructions
 - 2 labels* (1 for tube, 1 for form – both affixed)

*Different for ARI and Clearance Kits

Before Discharge – Nasal Swab Kit



- VTM in kits must stay refrigerated
 - Teach parents that VTM is “like milk”
- Mailing is pre-paid through USPS
- Sites must label all forms and vials before giving to parent

Follow-up Swab Types

All are sent (via regular USPS mail) to EMNet

- Clearance Swab
 - Taken by participants at home 3 weeks after admission

- ARI Swab
 - Taken by participant each time child has a breathing problem that results in a healthcare visit

- Summer Swab
 - Taken by participant during summer (June-August) when child is healthy

Clearance Swab Update

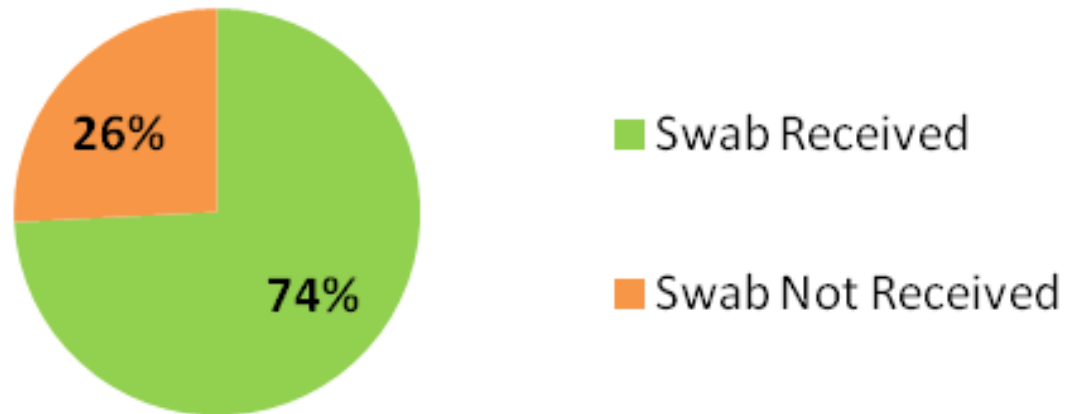
- The date that the clearance swab should be taken should be written on the swab kit

- Emphasize with parents:
 - The importance of the swabs
 - How to use the swab kits

Clearance Swab

Received swabs from 541 participants
(74%)

Goal is at least 80% for Year 3



What can sites do to help?

- Ensure all participants fully understand what enrolling in the study entails
- Emphasize the importance of the swabs to the study
- Enroll participants / families who are highly motivated to be in this cohort study

Enrollment Recap

1. Identify all children <1yr admitted with bronchiolitis during designated months of screening
2. Complete Screening Form, review Informed Consent, completed Medical Records Release Form, assign study ID, complete Intake Form, Contact Form and distribute Maternal P & N Form
3. Collect biological specimens (blood, NPA)
4. Collect index swab and teach technique to parent/guardian
5. Collect Maternal P & N Form
6. Distribute nasal swab kits to take home

Deviations/Adverse Events



- There are protocol deviation and adverse event forms in REDCap for you to use
- Major protocol deviations need to be reported by email to Ashley Sullivan (EMNet) within 48 hours. EMNet will report to Dr Togias (NIAID).
- Serious AE need to be reported by email to Ashley Sullivan within 24 hours. EMNet will report to Dr Togias (NIAID).

afsullivan@partners.org

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After Discharge

- Chart review portion of Intake Form
- Inpatient Form
- 1-week Follow-up Call
- PCP study introduction letter
- Virology result letters
- Readmissions for a breathing problem
- Annual search of medical records in your healthcare system

1-week Follow-up Form

- 10-minute follow-up phone call with parent 1 week after hospital discharge (8 to 14 days after hospital visit)
- Try calling
 - at least 5 times over
 - at least 3 days
- Always record attempted calls on the Follow-up Form

Run-in

- If 1-week follow-up call not completed (and no contact by EMNet at 3 weeks), the child will not be part of the “chronic cohort” (with long-term follow-up)
- Child will not count towards goal of 30 chronic cohort participants per site per year
- We estimate that 10% of study participants will not meet run-in requirements

Virology Results



- You will receive virology testing results within ~1 year of index hospitalization
- Send letters to:
 - Parent
 - PCP, if requested by parent

Readmissions

- Monitor fully enrolled participants for hospital readmissions related to a breathing problem until the child is age 1 year
- Complete Readmission Intake Form (interview) and Readmission Intake Chart Review
- Help complete ARI swab

Annual Records Review

- Each year, acquire available medical records in your hospital system
- Send records to EMNet for review
- If records are NOT available in your system, **EMNet** will request records directly from these “outside” providers and institutions
- Each participant must have a completed medical records release form uploaded in REDCap

REDCap Issues

- Problems logging in?
Contact Partners HealthCare EDC Support
edcsupport@partners.org
- New user requests, other issues, or questions?
Contact Courtney Tierney, MPH
cntierney@partners.org
617-643-7652

Questions?

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