The Respiratory Specimen Collection Trial (ReSpeCT): a randomized controlled trial comparing quality and timeliness of respiratory sample collection in the home by a parent or healthcare worker in children aged <2-years.

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Keywords: acute respiratory infections, nasal swabs, children, specimen collection, parent

Running title: Respiratory Specimen Collection Trial
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Summary: Parent sample collection during acute respiratory infections (ARIs) in children led to a similar proportion of ARIs with samples collected, at fewer days after ARI onset, and with higher likelihood of pathogen identification, compared to collection by healthcare workers.
ABSTRACT

Background Most acute respiratory infection (ARI) research focuses on severe disease, overlooking the burden of community-managed illness. For community-based studies, home-based specimen collection by parents could be a resource-saving alternative to healthcare worker (HCW) collection. We compared parent and HCW groups for likelihood of specimen collection, timeliness, and quality.

Methods In this unblinded randomized-controlled trial, parents from Brisbane, Australia, were taught to identify new ARI episodes in their children aged <2-years. With an ARI, parents either collected a nasal swab (P-group) or contacted a HCW who visited to obtain a nasopharyngeal swab (HCW-group). We compared likelihood and timeliness of specimen collection, and respiratory pathogen detection. A nested diagnostic study compared paired specimen collections from children in the HCW-group.

Results There were 76 incident ARI episodes from 31 children, and 102 episodes from 33 children, in the P- and HCW-groups, respectively. The proportion of ARIs for which a specimen was collected was similar (P-group: 69.7%, HCW-group 72.5%; p=0.77), with pathogens detected in 93.8% and 77.5% of specimens respectively (p=0.03). There was a shorter period between ARI onset and specimen collection in the P-group (mean difference (MD)=1.9-days; 95% confidence interval (CI): 0.7, 3.0; p<0.001). For the 69 paired specimens, viral load was lower in parent-collected swabs (Ct MD=4.5, 95%CI 3.1-5.9, p<0.001).

Conclusions Parents obtained samples in a similar proportion of ARIs, at fewer days after ARI onset, and with higher likelihood of pathogen identification than HCW sampling. This method
can be used in population-based epidemiological studies of ARI as a resource-saving alternative.

**Trial registration:**

The trial was registered with ClinicalTrials.gov (NCT00966069). The Queensland Children’s Health Services Ethics Committee (HREC/09/QRCH/42) approved the study.
INTRODUCTION

Acute respiratory infections (ARIs), the most frequent illnesses in childhood, caused a loss of >84.9 million disability-adjusted life-years globally in children aged <5-years in 2015 [1]. Viral ARIs in early childhood are also the major cause of acute asthma exacerbations and may play a role in asthma inception in high-risk, susceptible individuals [2-4]. Most ARI research focusses on severe disease, particularly hospitalizations, often overlooking the burden of community-managed disease and associated economic costs, the latter heavily influenced by work days lost by the parent or caregiver [5, 6]. Community-based research of ARIs in children is needed to capture the full spectrum of ARI severity, for comprehensive cost-effectiveness assessments of preventive and therapeutic options, and to improve understanding of the developing immune system [7].

Respiratory specimen collection in the home by household members may facilitate community-based ARI research; yet research on this topic is limited. A pilot randomized controlled trial (RCT) from the Netherlands last decade suggested swabs were almost twice as likely to be collected during an ARI by parents than healthcare workers (HCWs; 43% versus 24%) [8]. Additionally, parent-collected swabs were 1.2 times more likely to test positive for any virus (80% versus 67%). However, because of small subject numbers, neither of these differences was statistically significant [8]. Subsequently, the quality and acceptability of parent-collected nasal specimens for virus detection in young children has also been demonstrated [9-13], and several studies have used parental sampling, although without validation [14-16]. Studies with small numbers have involved parent and HCW swabs collected simultaneously from the same child [13] or within 24-hours of one another [17].
In order to prepare for a larger, community-based study [18-22], we sought to compare the likelihood and timeliness of swab obtainment, as well as the quality of specimens collected by parents and HCWs. Our primary hypothesis was that allocation to a parent-collected nasal swab specimen group would increase the proportion of identified ARIs for which a specimen was collected when compared to HCW nasopharyngeal specimens.
METHODS

Study design and study subjects

We conducted a parallel-group RCT to compare the relative proportions, timeliness, and quality of parent-collected nasal swabs versus HCW-collected nasopharyngeal swabs during an ARI episode. Within the HCW-arm of the study we also conducted a nested diagnostic study to compare the quality and diagnostic performance of the swabs collected by parents and HCWs at the same time from the same child. Children were eligible for the study if they were healthy, living in Brisbane (a subtropical capital city in Australia) without chronic disease, born at ≥36-weeks gestation, and aged <2-years between September 01 2009 and February 26 2010.

Randomized controlled trial component

At the enrolment (initial) visit, after obtaining written informed consent from a parent or guardian, children were randomized into a parent-collected (P-group) or HCW-collected group (HCW-group) in a 1:1 ratio.

During the initial visit all parents were taught by a study nurse how to: (i) recognize symptoms of an ARI, (ii) complete a daily symptom diary, and (iii) collect an anterior nasal specimen [15, 16, 18].

Parents were taught to keep a daily symptom diary for the study child and to identify when a new (at least three symptom-free days from the previous episode) ARI occurred. An ARI was defined as the presence of at least one (fever, wheezing, shortness of breath, pulmonary congestion, moist cough, pneumonia, ear infection) or two (nasal discharge or congestion,
sore throat, cough, muscle aches, chills, headache, irritability, decreased activity, or vomiting) specific symptoms [15, 16].

When an ARI occurred, those in the P-group were asked to obtain an anterior nasal swab and mail it back to the research laboratory. Those in the HCW-group were asked to notify research staff to make an appointment for a home visit for collection of a nasopharyngeal swab (NPS) as soon as possible. These NPS specimens were returned by the HCW to the research laboratory immediately following the home visit.

The primary outcome for the RCT was the proportion of identified ARIs for which a specimen was collected in the P-group and the HCW-group. Secondary outcomes were the timeliness and quality of swab obtainment. Timeliness of swab return was measured as the number of days between the onset of an ARI and when the specimen was collected. We measured specimen quality in two ways: firstly, by comparing the likelihood of pathogen identification, and secondly, by comparing the endogenous retrovirus 3 (ERV3, a marker of human DNA) load using semi-quantitative estimates of viral load determined by real-time polymerase chain reaction (PCR) assay cycle threshold (Ct) values.

**Nested diagnostic study component**

When a child in the HCW-group received a home-visit following a reported ARI, the child had two specimens collected from different nostrils: a NPS specimen by the HCW from one nostril (described as part of the RCT study component) and an anterior nasal swab by a parent from the other nostril. The anterior nasal swab was mailed back to the research laboratory.
The primary outcome measure for the nested diagnostic study was the proportion of specific agreement of pathogen detection in paired swabs. The secondary outcome was the agreement in ERV3 loads between parent-collected and HCW-collected swabs [18].

**Laboratory testing**

All study swabs received in the laboratory were catalogued and stored at -80°C until they underwent analysis. As described elsewhere [9, 18, 23], stored specimens were thawed and tested by PCR assays for sample quality using ERV3, 17 respiratory viruses, and three bacteria. Ct values from positive real-time PCR assays are inversely proportional to the amplified ERV3 nucleic acid in the NPS sample and provide a semi-quantitative estimate of viral load [23].

**Sample size**

The sample size calculation was based on the primary outcome of interest for the RCT component of the study, which was the difference between the proportions of identified ARIs for which a specimen was collected in the two groups. In order to show a difference of 25 percentage points, we estimated 60 subjects (30 per group) were required (power: 80%, alpha: 0.05). This was based on the following assumptions: an average of four ARIs per subject over the course of the study, an intraclass correlation coefficient within individuals of 0.15 [16, 24], specimen collection in 50% of the ARI episodes in the HCW-collected group [8], attrition of 25% in each group, and 80% usable symptom diary data.

**Data analyses**
Descriptive analyses of demographic and clinical data are presented (by group) as either frequencies with proportions, means with standard deviation (sd), or medians with interquartile range (IQR), and compared by chi-square test, t-test, or Poisson regression, depending on distribution of the data. From the symptom diary data we calculated a crude prevalence of symptoms as the number of days with symptoms in relation to the total number of days provided. We determined the number of incident ARIs (ARI events present at the initial visit were excluded), and the duration of ARIs (total and the average per participant), as well as ARI rates per child-year. The mean durations of ARI episodes in the P- and HCW-groups were compared using a generalized linear model with Gaussian family and identity link. Robust variance estimates were calculated with sandwich estimators used to account for repeated episodes within children. Effect estimates are presented as the mean between-group difference with 95% confidence intervals (95%CI). ARI rates in the P- and HCW-groups were compared using Poisson regression, with effect estimates presented as incidence rate ratios with 95%CI.

For the RCT component of the analysis we excluded swabs that could not be linked to an ARI episode based on the symptom diary data (no data available or swab obtained >7-days after the first day of an ARI episode). We analyzed the first swab if more than one swab was obtained during the same ARI episode. The association between group and proportion of identified ARIs with a swab collected and between group and proportion of swabs with a pathogen/virus/bacteria positive finding were estimated using generalized linear models with binomial family and identity link with robust variance estimates. The association between group and timeliness and between group and ERV3 Ct values of swabs was estimated using a
generalized linear model with Gaussian family and identity link. Effect estimates are presented as absolute between-group mean differences (95%CI).

For the diagnostic test component of the analysis, we analyzed swab pairs obtained from the same child at the same visit in the HCW group. We performed descriptive analyses of the detection of no, any, and the same pathogens in swab pairs. The positive agreement (PA) was calculated using the formula $PA = 2a/|2a+b+c|$ and the negative agreement (NA) as $NA = 2d/|2d+b+c|$, where a, b, c, d are the standard cell labels for a 2x2 table [25]. Agreement was classified according to the scale suggested by Landis and Koch (1977) for Cohen’s kappa [26]. Asymptotic 95%CIs were calculated based on standard errors that were calculated using the formulae given by Mackinnon 2000 [27] (see supplementary material). We further compared the ERV3 Ct values of paired swabs using a generalized linear model with Gaussian family and identity link. Additionally, we calculated the mean difference of the ERV3 Ct values between paired swabs and used the limits of agreement method for assessing the agreement between them [28]. Analyses were performed with Stata for Windows, version 12 (StataCorp, College Station, TX) and Microsoft Excel 2010 for Windows 2010. A fuller description of recruitment, randomization, study procedures, laboratory testing, and data analyses is provided in the supplementary material.

The trial was registered with ClinicalTrials.gov (NCT00966069). The Queensland Children’s Health Services Ethics Committee (HREC/09/QRCH/42) approved the study.
RESULTS

Overall, 126 children were assessed for eligibility, of whom 64 children were randomized: P-group: 31, HCW-group: 33 (Figure 1). Overall, the sociodemographic characteristics were similar in the two groups (Table 1).

Participants provided 10,944 days of daily symptom data (P-group: 4,835, HCW-group: 6,109; average days per child, P-group: 156.0; HCW-group: 185.1 (student’s t-test p=0.27)). Seven children provided no data (P-group: 4, HCW-group: 3), specimens collected from these children were excluded from further analyses (Figure 1). At least one solicited symptom was reported from children on 27% of total study days (2,916 child-days). The most common symptom was nasal discharge (19% of all study days), followed by cough (11%).

Study children experienced 178 incident ARI episodes (P-group: 76, HCW-group: 102). Incidence and duration of ARI were similar in both groups (Table 1).

Randomized controlled trial

There were 53 (P-group) and 74 (HCW-group) swabs available during 76 and 102 incident ARI episodes, respectively, resulting in a similar proportion of incident ARIs for which a specimen was collected (69.7% versus 72.5%; mean difference=2.8%; 95%CI: -6.2, 21.8; p=0.77) (Table 2). No safety issues were reported regarding swab collection. There was a significantly shorter average period between ARI onset and obtaining specimens in the P-group (mean: 3.0 days; sd: 2.7) than HCW-group (mean: 4.9; sd: 2.8 days; mean difference=1.9 days; 95%CI: 0.7, 3.0; p<0.001). Swabs collected in the P-group had higher ERV3 Ct values (lower ERV3 loads) than HCW-collected swabs (Table 2). The proportion of swabs with any pathogen detected during incident ARIs and the proportion of swabs with any bacteria detected during incident ARIs was
higher in the P-group (P-group versus HCW-group: any pathogen 93.8% vs. 77.5%; any bacteria 91.7% vs. 73.2%; Table 2).

**Nested diagnostic study**

From the 74 paired swabs obtained in the HCW-group, 69 pairs could be analyzed for viruses and bacteria. Of these, in four swab pairs (6%) no pathogen was identified and in 47 swab pairs (68%) in both swabs at least one pathogen was identified.

The positive and negative agreement for at least one pathogen, at least one virus, and at least one bacteria detected were: 0.84 (95%CI: 0.77, 0.91) and 0.31 (95%CI: 0.08, 0.54); 0.63 (95%CI: 0.46, 0.81) and 0.85 (95%CI: 0.77, 0.92); and 0.82 (95%CI: 0.74, 0.90) and 0.39 (95%CI: 0.17, 0.60), respectively. Further results for single pathogen findings are shown (Table 3).

The mean ERV3 Ct value was higher (lower load) in parent-collected nasal swabs (31.2, sd: 4.8) than HCW-collected NPS specimens (26.7; sd: 2.6; mean difference= -4.5; 95%CI: -5.9, -3.1; p<0.001). Figure 2 is a Bland-Altman plot displaying the difference in viral load between paired observations. The 95% limits of agreement were -12.3 to 3.3.
Discussion

Studying ARIs is important, not only for their direct impact on health and economic burden, but also because of their influence on chronic lung disease, and the increasing recognition of their role in the ontogeny of the developing human immune system. Respiratory specimen collection in the home conducted by household members may facilitate studies in this field as a resource-saving and potentially bias-reducing alternative to collection by HCWs. This offers the possibility of richer studies to assess pathogen acquisition at various life stages, and the role viruses and bacteria play in respiratory health.

In our study, sampling by parents led to a decrease in the time between ARI onset and swab collection which is thought to improve virus detection [11]. Whilst our overall virus detection rate was similar to a study of rhinitis episodes in children attending childcare [29], it was lower than reported in other similar studies [11, 12, 24]. The bacterial detection rate was similar to other upper airway studies in young children [30], and higher than reported in adults [31].

Our results did not confirm our primary hypothesis, which was based on the RCT findings in Dutch infants [8] as specimen collection by parents did not increase the swab obtained proportion, compared to collection by a HCW. A possible reason for this could be cultural and methodological differences: in two other Australian studies, sample collection was similarly high [11] or even higher [24]. Van der Zalm and colleagues suggested lower swab obtainment proportions in the HCW-group might be caused by parents being too busy to call or simply forgetting to call the study coordinator. However, we did not see these lower proportions in the HCW-group in our study. Differences between these studies included the age of the children and the sampling method. Children in our study were slightly older (up to age 2-years) than those in the Dutch RCT, where infants were followed during their first year of life. Further,
Australian parents were asked to take an anterior nasal swab, whereas Dutch parents were expected to obtain a more invasive nasopharyngeal mucus sample, which might be expected to lead to a lower proportion of sampling initially and in subsequent ARIs. Parents in our study were also aware of the research question, which may not have been the case in the Dutch study.

Whilst self- or parent-collection of specimens is now common in research, there has been little published about how specimens are returned to the laboratory once collected. Virus and bacteria detection was demonstrably better in the parent-collection arm of this study where specimens were mailed back to the laboratory using the standard postal service. In a previous study, we compared paired specimens collected in Central Australia at the same time from the same individual either frozen immediately for the journey or returned by air and surface mail at ambient temperature to our laboratory. We found no impact of overall virus detection despite the difference in maximum temperature experienced in transit for each set of swabs: frozen -5°C, surface mail +30°C [32]. However, we did find that bacterial detection appeared to be reduced in the mailed specimens [33]. This is at odds with a recent paper from Western Australia, which found exposure to ambient conditions (maximum temperature during the study: +33°C) for up to 14-days and parent-collection did not result in reduced bacterial detection in specimens collected from 20 in-hospital very premature infants [34]. Further work is required to assess the impact of specimen transport from the home to the laboratory on specimen quality and pathogen detection.

Although parents were trained in identifying the start of an ARI episode it is not clear if they identified every ARI episode correctly. Some episodes had multiple swabs collected although parents were asked to collect one swab per episode, as early as possible after the start.
Consequently, in cases where no samples were received during an ARI episode, we were unable to determine whether this was from missed sampling or due to not having identified the start of an ARI episode. However, as this occurred in both groups it should not have interfered with overall conclusions.

Our results provide support that parents can collect specimens, with simple training, suitable for pathogen analysis in community-based studies. A key advantage of parental sampling, compared with collection by HCWs or trained research staff, is lower costs from a reduced need for HCW home visits. Further, compliance should improve as self-collection and mailing swabs is easier and less time-consuming than arranging a timely home visit convenient for both parents and staff. Our findings of substantial positive and almost perfect negative agreement for the detection of any virus between paired swabs obtained from the same child at the same visit by a parent (anterior nasal swab) and by a HCW (NPS specimen) were slightly lower for the positive agreement (0.85, calculated from the numbers provided), but better in terms of negative agreement (0.39) than reported in a Hong Kong study comparing the finding of five viruses in nasal swab and nasopharyngeal aspirate specimens [35].

For rhinoviruses we observed a slight positive and an almost perfect negative agreement between parent-and HCW-collected swabs, meaning that rhinoviruses were more often detected in parent-collected swabs, which might have been due to the different sampling sites. Although, point inoculation of rhinovirus suspension in adult volunteers led to higher virus recovery rates in the nasopharynx than in the turbinates [36]. The almost perfect positive agreement and fair negative agreement for any bacteria detected is supported by findings from other studies [37].
Interestingly, Ct values for ERV3 in the parent-collected swabs were higher (lower load) than HCW-collected swabs. However, the Ct values were still reasonable in the parent-collected specimens [9]. Further studies of this nature are required to better understand the role of sample quality and collection site on pathogen detection.

In summary, our results did not show sampling by parents to be superior to sampling by a HCW in terms of proportions of incident ARIs for which a specimen was collected. We found parents collect specimens earlier in the course of the ARI episode and that these samples have higher pathogen yields. Consequently, having parents collecting nasal swab specimens from young children is a potential resource-saving strategy when undertaking population-based studies on viral infections.

**FUNDING**

This study was supported by a grant from the Children’s Hospital Foundation Queensland (grant no. 10290) and by a doctoral fellowship of the German Academic Exchange Service (DAAD).

**ACKNOWLEDGEMENTS**

We would like to thank the nursing, laboratory, and other research staff who assisted with this study.
REFERENCES


Table 1: Sociodemographic characteristics of the study subjects and number and duration of incident acute respiratory infection (ARI) episodes, by group (P-group=parent collection group, HCW-group=health care worker collection group)

<table>
<thead>
<tr>
<th></th>
<th>P-group (N=31)</th>
<th>HCW-group (N=33)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)) or mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>15 (48.4)</td>
<td>18 (54.5)</td>
<td>0.62</td>
</tr>
<tr>
<td>Mean (standard deviation) age at study entry (first visit) in months</td>
<td>15.6 (6.3)</td>
<td>15.2 (5.0)</td>
<td>0.78</td>
</tr>
<tr>
<td>Ever breastfed</td>
<td>27 (87.1)</td>
<td>31 (93.9)</td>
<td>0.26</td>
</tr>
<tr>
<td>Child ever received influenza vaccine</td>
<td>5 (16.1)</td>
<td>5 (15.2)</td>
<td>0.86</td>
</tr>
<tr>
<td>(P-group: n=30, HCW-group: n=31)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No childcare*</td>
<td>14 (45.2)</td>
<td>12 (36.4)</td>
<td>0.56</td>
</tr>
<tr>
<td>Number of adults (≥16-years) in the household, median (IQR)</td>
<td>2 (2-2)</td>
<td>2 (2-2)</td>
<td>0.57</td>
</tr>
<tr>
<td>Number of other children (aged &lt;16-years) belonging to the</td>
<td>1 (0-1)</td>
<td>1 (0-2)</td>
<td>0.05</td>
</tr>
<tr>
<td>household, median (IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No smoking adults in household</td>
<td>24 (77.4)</td>
<td>24 (72.7)</td>
<td>0.62</td>
</tr>
<tr>
<td>Primary carer employed</td>
<td>18 (58.1)</td>
<td>19 (57.6)</td>
<td>0.97</td>
</tr>
<tr>
<td>Income (AUD$)†</td>
<td></td>
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<td>----------------</td>
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<tr>
<td>&lt;$26,000</td>
<td>4 (12.9)</td>
<td>2 (6.1)</td>
<td>0.71</td>
</tr>
<tr>
<td>$26,000-$52,000</td>
<td>7 (22.6)</td>
<td>6 (18.2)</td>
<td></td>
</tr>
<tr>
<td>$52,000-$94,000</td>
<td>10 (32.3)</td>
<td>11 (33.3)</td>
<td></td>
</tr>
<tr>
<td>≥$94,000</td>
<td>10 (32.3)</td>
<td>14 (42.4)</td>
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</tr>
</tbody>
</table>

Incident ARI episodes (number and duration)

<p>| | | | |</p>
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Person-days contributed</td>
<td>4835</td>
<td>6109</td>
<td>0.27</td>
</tr>
<tr>
<td>Number of incident ARI episodes</td>
<td>76</td>
<td>102</td>
<td></td>
</tr>
<tr>
<td>Mean duration (standard deviation) of an ARI episode (days)</td>
<td>9.9 (12.6)</td>
<td>11.1 (17.0)</td>
<td>0.61</td>
</tr>
<tr>
<td>ARI incidence rate per child-year (95%CI)</td>
<td>6.9 (5.5, 8.7)</td>
<td>7.4 (6.1, 9.0)</td>
<td>0.33</td>
</tr>
</tbody>
</table>

*No childcare if neither formal (regulated care outside the child’s home) nor informal (non-regulated care provided by family or friends) care

†Income categories based on 2009 Australian Bureau of Statistics income quartiles [38].
Table 2: Number and proportion of specimens returned at incident acute respiratory infection (ARI) episodes, ERV cycle threshold (Ct) values, and pathogen detection, by group (P-group=parent collection group, HCW-group=health care worker collection group)

<table>
<thead>
<tr>
<th></th>
<th>P-group</th>
<th>HCW-group¹</th>
<th>Mean difference (95%CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=28)</td>
<td>(n=29)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Specimen collected during incident ARI episodes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of specimens collected (x) during incident ARI episodes (y), x/y</td>
<td>53/76</td>
<td>74/102</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage of incident ARIs for which a specimen was collected</td>
<td>69.7%</td>
<td>72.5%</td>
<td>2.8% (-6.2, 21.8)</td>
<td>0.77</td>
</tr>
<tr>
<td><strong>Timeliness of specimen collection</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days between ARI symptom onset and specimen collection, mean (sd)</td>
<td>3.0 (2.7)</td>
<td>4.9 (2.8)</td>
<td>1.9 (0.7, 3.0)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Quality of specimen collection</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ERV3 Ct value (sd)</td>
<td>31.1 (3.6)</td>
<td>27.1 (3.0)</td>
<td>-4.0 (-5.6, -2.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Percentage of incident ARIs with a pathogen positive swab available</td>
<td>59.2%²</td>
<td>53.9%³</td>
<td>-5.3% (-25.5, 14.9)</td>
<td>0.61</td>
</tr>
<tr>
<td>Percentage of swabs with any pathogen detected during incident ARIs</td>
<td>93.8%</td>
<td>77.5%</td>
<td>-16.3% (-31.1, -1.5)</td>
<td>0.03</td>
</tr>
<tr>
<td>Percentage of swabs with any virus detected during incident ARIs</td>
<td>41.7%</td>
<td>29.6%</td>
<td>-12.1% (-26.9, 2.7)</td>
<td>0.11</td>
</tr>
<tr>
<td>Percentage of swabs with any bacteria detected during incident ARIs</td>
<td>91.7%</td>
<td>73.2%</td>
<td>-18.4% (-33.1, -3.8)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

1 refers to HCW-collected nasopharyngeal specimens only, not parent-collected anterior nasal swabs

2 76 incident ARIs, 53 swabs collected, 48 swabs could be analyzed, 45 swabs positive for any pathogen

3 102 incident ARIs, 74 swabs collected, 71 swabs could be analyzed, 55 swabs positive for any pathogen
Table 3: Agreement in pathogen detection in 69 paired nasal swabs (parent-collected nasal swab and HCW-collected nasopharyngeal specimen) obtained within the HCW-group

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Parent-collected swab positive, HCW-collected swab negative (N)</th>
<th>Parent-collected swab negative, HCW-collected swab positive (N)</th>
<th>Parent- and HCW-collected swabs positive (N)</th>
<th>Parent- and HCW-collected swabs negative (N)</th>
<th>Positive agreement (95%CI)</th>
<th>Negative agreement (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least one pathogen identified</td>
<td>12</td>
<td>6</td>
<td>47</td>
<td>4</td>
<td>0.84 (0.77, 0.91)</td>
<td>0.31 (0.08, 0.54)</td>
</tr>
<tr>
<td>At least one virus identified</td>
<td>9</td>
<td>6</td>
<td>13</td>
<td>41</td>
<td>0.63 (0.46, 0.81)</td>
<td>0.85 (0.77, 0.92)</td>
</tr>
<tr>
<td>At least one bacteria identified</td>
<td>13</td>
<td>6</td>
<td>44</td>
<td>6</td>
<td>0.82 (0.74, 0.90)</td>
<td>0.39 (0.17, 0.60)</td>
</tr>
<tr>
<td>Viruses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhinovirus</td>
<td>10</td>
<td>1</td>
<td>1</td>
<td>57</td>
<td>0.15 (0.00, 0.42)</td>
<td>0.91 (0.86, 0.96)</td>
</tr>
<tr>
<td>Parainfluenza virus III</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>66</td>
<td>0.5 (0, 1.00)</td>
<td>0.99 (0.96, 1.01)</td>
</tr>
<tr>
<td>Respiratory syncytial virus A</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>67</td>
<td>0.67 (0.05, 1.00)</td>
<td>0.99 (0.98, 1.00)</td>
</tr>
<tr>
<td>Respiratory syncytial virus B</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>67</td>
<td>1 (1.00, 1.00)</td>
<td>1 (1.00, 1.00)</td>
</tr>
<tr>
<td>Pathogen</td>
<td>Detected</td>
<td>Positive</td>
<td>Total</td>
<td>True</td>
<td>95% CI</td>
<td>99% CI</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>----------</td>
<td>----------</td>
<td>-------</td>
<td>------</td>
<td>------------</td>
<td>------------</td>
</tr>
<tr>
<td><strong>Human coronavirus NL63</strong></td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>68</td>
<td>1 (1.00, 1.00)</td>
<td>1 (1.00, 1.00)</td>
</tr>
<tr>
<td><strong>Human coronavirus HKU1</strong></td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>68</td>
<td>0 (0.00, 0.00)</td>
<td>0.99 (0.98, 1.01)</td>
</tr>
<tr>
<td><strong>Human metapneumovirus</strong></td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>68</td>
<td>0 (0.00, 0.00)</td>
<td>0.99 (0.98, 1.00)</td>
</tr>
<tr>
<td><strong>Adenoviruses</strong></td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>65</td>
<td>0 (0.00, 0.00)</td>
<td>0.97 (0.94, 1.00)</td>
</tr>
<tr>
<td><strong>Human polyomavirus WUV</strong></td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>65</td>
<td>0.40 (0.00, 0.94)</td>
<td>0.98 (0.95, 1.00)</td>
</tr>
<tr>
<td><strong>Human polyomavirus KIV</strong></td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>63</td>
<td>0.5 (0.08, 0.92)</td>
<td>0.97 (0.94, 1.00)</td>
</tr>
<tr>
<td><strong>Human bocavirus-1</strong></td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>68</td>
<td>1 (1.00, 1.00)</td>
<td>1 (1.00, 1.00)</td>
</tr>
<tr>
<td><strong>Bacteria</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>10</td>
<td>10</td>
<td>18</td>
<td>31</td>
<td>0.64 (0.50, 0.79)</td>
<td>0.76 (0.65, 0.86)</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>13</td>
<td>6</td>
<td>32</td>
<td>18</td>
<td>0.77 (0.67, 0.87)</td>
<td>0.65 (0.51, 0.80)</td>
</tr>
<tr>
<td><em>Moraxella catarrhalis</em></td>
<td>16</td>
<td>11</td>
<td>27</td>
<td>15</td>
<td>0.67 (0.55, 0.79)</td>
<td>0.53 (0.37, 0.68)</td>
</tr>
</tbody>
</table>

Influenza virus A, influenza virus B, parainfluenza virus I, parainfluenza virus II, human coronavirus OC43, and human coronavirus 229E were not found in any swab.
Figure 1: Trial profile (HCW=health care worker, NPS=nasopharyngeal swab)

126 assessed for eligibility

62 excluded
- 40 declined to participate
- 3 age > 2 years
- 4 born < 36-weeks gestational age
- 2 chronic pulmonary or cardiovascular disorders
- 9 moved/about to move out of region
- 3 had insufficient English skills
- 1 other reason

64 randomized

31 assigned to parent-collection group

3 provided no symptom data

28 included in analysis

Randomised controlled trial: Quality and timeliness of specimen collection performance

33 assigned to HCW-collection group

4 provided no symptom data

29 included in analysis

Diagnostic study: Pathogen identification HCW-collected NPS vs parent-collected dry swab (same child)
Figure 2: Bland-Altman plot displaying the difference in ERV3 cycle threshold (Ct) values between paired nasal swabs (parent-collected nasal swab and HCW-collected nasopharyngeal specimen) obtained within the HCW-group (n=62)