An Evaluation of Arsenic Exposure as a Risk Factor for Pneumonia in Pediatric Populations in Rural Bangladesh

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Overview

1. Arsenic and Respiratory Diseases
2. Study Design
3. Results
4. Discussion
5. Future Research
Arsenic and Respiratory Outcomes

There is a growing body of literature linking chronic arsenic exposure and respiratory related outcomes

• Reduced lung function
• Cough
• Breathing problems

Less Conclusively

• Lower respiratory tract infections
• Bronchitis
• Pulmonary tuberculosis mortality

Arсеник и симптомы дыхания

Опасность для взрослых участников, сообщающих об проблемах дыхания, при различных уровнях концентрации арсената в воде в течение 4 лет наблюдения в Клинике здравоохранения Арсенитной Лонгитюдная Студия (HEALS) из 11,746 участников, учитывая их возраст, пол, массу тела, образ жизни, кожные болезни и статус смены.

<table>
<thead>
<tr>
<th>Водный арсенат (мкг/л)</th>
<th>Хронический кашель HR (95% CI) n=859</th>
<th>Нарушения дыхания HR (95% CI) n=1169</th>
<th>Кровь в мокроте HR (95% CI) n=238</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤7</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>7—40</td>
<td>1.19 (0.95 to 1.50)</td>
<td>1.44 (1.20 to 1.74)</td>
<td>1.15 (0.75 to 1.76)</td>
</tr>
<tr>
<td>40—90</td>
<td>1.40 (1.11 to 1.75)</td>
<td>1.52 (1.25 to 1.84)</td>
<td>1.09 (1.69 to 1.70)</td>
</tr>
<tr>
<td>90—178</td>
<td>1.57 (1.25 to 1.97)</td>
<td>1.42 (1.16 to 1.73)</td>
<td>1.66 (1.10 to 2.51)</td>
</tr>
<tr>
<td>&gt;178</td>
<td>1.60 (1.27 to 2.01)</td>
<td>1.41 (1.56 to 1.72)</td>
<td>1.51 (0.98 to 2.32)</td>
</tr>
</tbody>
</table>

*Расчеты выполнены на основе моделей пропорциональной опасности Коса.*
## Arsenic and Lower Respiratory Tract Infection (LRTI)

Relative Risks (RR) for episodes of LRTI among the infants in relation to maternal urinary arsenic (GW8 and GW30): 2002–2003 pregnancy cohort of 1552 infants in Matlab, Bangladesh

<table>
<thead>
<tr>
<th>Arsenic levels in quintiles (µg/L)(^a)</th>
<th>Person-weeks of recall</th>
<th>LRTI</th>
<th>Severe LRTI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of episodes</td>
<td>RR (95% CI)</td>
<td>Adjusted RR (95% CI)(^b)</td>
</tr>
<tr>
<td>Average(^c)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 39(^d)</td>
<td>3,380</td>
<td>134</td>
<td>1</td>
</tr>
<tr>
<td>39–64</td>
<td>3,394</td>
<td>172</td>
<td>1.28 (1.02–1.60)</td>
</tr>
<tr>
<td>65–132</td>
<td>3,309</td>
<td>185</td>
<td>1.41 (1.13–1.76)</td>
</tr>
<tr>
<td>133–261</td>
<td>3,198</td>
<td>215</td>
<td>1.69 (1.37–2.10)</td>
</tr>
<tr>
<td>≥ 261</td>
<td>3,269</td>
<td>237</td>
<td>1.83 (1.48–2.26)</td>
</tr>
</tbody>
</table>

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A. Sum of inorganic and methylated arsenic species. B. Test for linear trend p < 0.05 for all exposures levels (GW8, GW30, and average) except diarrhea for GW30, adjusted for mother’s education, asset index, parity, BMI, gestational age, and infant’s sex. C. Mean urinary arsenic concentrations at GW8 and GW30. D. Reference group.

LRTI was mother reported defined as cough and/or difficult breathing combined with rapid respiration in the past 7 days. Severe LRTI was defined as symptoms of LRTI accompanied by chest in-drawing.

Reference: Rahman et al. 2011
Limitations of Previous Studies

- Use self-reported rather than physician diagnosed respiratory illness
- Most studies have been conducted in adult populations
Human Studies in Populations with Chronic Arsenic Exposure

- Reduced percentage of CD4 T cells and interleukin (IL) -2 secretion levels in Mexico
- Reduced T-cell proliferation and cytokine secretion (TNF-α, Interferon-γ, IL-2, IL-10) in West Bengal, India
- Lower breast milk concentrations of IL-7 and lactoferrin in Bangladesh

References: Soto-Pena et al., 2006; Stepnik et al., 2005; Conde et al., 2007; Raqib et al. 2009; Biswas et al., 2008; Ahmed et al. 2011
Arsenic Exposure and Immunosuppression

Animal Studies (with arsenate)
• Inhibition T cell formation

In vitro studies (with arsenite)
• Decreased IL-2 secretion and cell proliferation
• Decreased T cell activation

References: Soto-Pena et al., 2006; Stepnik et al., 2005; Conde et al., 2007; Raqib et al. 2009; Biswas et al., 2008
Pneumonia Etiology Research for Child Health Project (PERCH)

The PERCH project is a large multi-country case-control study of severe pneumonia in hospitalized children under five years of age.

Leading Global Cause of Under 5 Deaths in 2010

1.4 Million Pneumonia Deaths

Overall PERCH Objective

Determine the etiology and associated risk factors of severe or very severe pneumonia hospitalized in children 28 days to 59 months of age.

PERCH Risk Factors

- Breastfeeding
- Malnutrition
- Childcare
- Socioeconomic status
- Water and sanitation access
- Past morbidities
- Vitamin A supplementation
- Vaccination history
Investigate if exposure to arsenic during childhood is a significant risk factor for pneumonia in children under five years of age
Study Area

Matlab Health and Demographic Surveillance System (HDSS)
220,000 individuals

International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b)
70% of the 13,286 wells in the Matlab HDSS contain arsenic exceeding WHO guideline of 10 µg/L.

References: Rahman et al. 2006 et al.; van Ginneken et al. 1998
Study Design

Nested Case Control Study
- January 2012 - December 2013

Hospital Based Pneumonia Surveillance
Matlab icddr,b Hospital

Cases
153 Children
Severe or Very Severe Pneumonia Cases

Controls
296 Children
Age Matched Community Controls
PERCH Pneumonia Case Definition

Children 28 days to 59 months of age with Physician diagnosed World Health Organization defined severe or very severe pneumonia

Severe Pneumonia
• Child presenting with a cough or difficulty breathing
• Lower chest wall indrawing

Very Severe Pneumonia
• Child presenting with a cough or difficulty breathing
Any of the following
• Central cyanosis
• Unable to feed
• Vomiting everything
• Convulsions
• Lethargy or impaired consciousness
• Head nodding

Inclusion Criteria
• 28 Days to 59 Months of Age
• Child presents with cough or difficulty breathing
• Living in Matlab HDSS catchment area

Exclusion Criteria
• Admitted overnight to hospital in the last 14 days
• Child had been discharged from the hospital in the past 30 days as a PERCH case

PERCH Controls Inclusion/Exclusion Criteria

Inclusion Criteria
- 28 Days to 59 Months of Age
- Living in Matlab HDSS catchment area

Exclusion Criteria
- Child had been hospitalized in the past 14 days
- Child had been discharged from the hospital in the past 30 days as a PERCH case
- Child appeared very sick requiring urgent medical attention
- Child had severe or very severe pneumonia

12 Age Matched Community Controls Selected Per Month
- 28 days to <6 months, 6 to <12 months, 12 to <24 months, 24-59 months
Study Procedures

**Case Enrollment**
- Arrives to icddrb Hospital
- Hospital Screening For Eligibility

**Hospital Timepoint**
- Hospital Clinical Assessment & Specimen Collection

**Convalescent Timepoint**
- 30 Day Hospital Follow-up & Specimen Collection
Study Procedures

Community Control Enrollment

- Age Match Control Selected from HDSS
- Home Screening For Eligibility
- Hospital Clinical Assessment & Specimen Collection
Clinical Assessment and Specimen Collection

Clinical Assessment
• Anthropometric measurements
• Respiratory and heart rate
• Oxygen saturation by pulse oximetry
• Chest X-Ray

Specimen Collection
• Urine
• Induced sputum
• Blood
• Gastric Aspirate
Exposure Assessment

**Total Urinary Arsenic Analysis**
- Graphite furnace atomic absorption

**Cases Urine Collection**
- Hospital Admission Timepoint
- Convalescent Timepoint (30 Day Hospital Follow-up)

**Controls Urine Collection**
- Hospital Visit Timepoint
## Study Population Characteristics

**Table 1. Characteristics of the Study Population by Case Status**

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Cases</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of Children</strong></td>
<td>296</td>
<td>153</td>
<td></td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td>161</td>
<td>98</td>
<td></td>
</tr>
</tbody>
</table>
| **Age (Months) (Median ± SD  
(Range))**                    | 11±14.6(<1-58) | 12±12.80 (<1-51) | 0.90 |
| **Case Definition**          |          |       |          |
| Severe Pneumonia             | -        | -     | 88%      |
| Very Severe Pneumonia        | -        | -     | 12%      |
| **Paternal Education**       |          |       |          |
| No Formal Education          | 12%      | 18%   |          |
| 1-5 years                    | 21%      | 22%   |          |
| 5-10 years                   | 47%      | 49%   |          |
| Greater than 10 Years        | 20%      | 10%   |          |

*Control and cases compared using a two sample t-test for continuous variables and chi-square test for categorical variables*
## Study Population Characteristics

### Table 1. Characteristics of the Study Population (Cont.)

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th></th>
<th>Cases</th>
<th></th>
<th></th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>N</td>
<td>%</td>
<td>N</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Breastfed in the prior week</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exclusive</td>
<td>24%</td>
<td>71</td>
<td>22%</td>
<td>33</td>
<td></td>
<td>0.50</td>
</tr>
<tr>
<td>Mixed</td>
<td>55%</td>
<td>161</td>
<td>58%</td>
<td>89</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>21%</td>
<td>61</td>
<td>20%</td>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>WHO Weight for Height (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>z-score less than -2 SDs (wasting)</td>
<td>11%</td>
<td>33</td>
<td>20%</td>
<td>31</td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>z-score greater or equal to -2 SDs</td>
<td>89%</td>
<td>259</td>
<td>80%</td>
<td>122</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Main Source of Drinking Water</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Piped water</td>
<td>1%</td>
<td>4</td>
<td>3%</td>
<td>5</td>
<td></td>
<td>0.69</td>
</tr>
<tr>
<td>Deep Tubewell</td>
<td>2%</td>
<td>5</td>
<td>0%</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shallow Tubewell</td>
<td>96%</td>
<td>277</td>
<td>95%</td>
<td>145</td>
<td></td>
<td></td>
</tr>
<tr>
<td>River, stream, pond, lake</td>
<td>1%</td>
<td>4</td>
<td>2%</td>
<td>3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Control and cases compared using a two sample t-test for continuous variables and chi-square test for categorical variables
Urinary Creatinine

*\(p\)-value <0.05, Control and case timepoints compared using a two sample t-test
Time from Enrollment to Urine Collection

*P-value < 0.001, Control and case hospital timepoints compared using a two sample t-test
Exposure Assessment

* p-value <0.05, Control and case timepoints compared using a two sample t-test
Results

Case Enrollment

- Arrives to icddrb Hospital
- Hospital Screening For Eligibility
- Hospital Clinical Assessment & Specimen Collection
- Hospital Timepoint
- Convalescent Timepoint
- 30 Day Hospital Follow-up & Specimen Collection
## Results

### Table 3A. Crude and Adjusted Odds Ratios of Pneumonia Cases (Severe and Very Severe) for Case (Hospital Admission Timepoint) and Control Urine Samples*

<table>
<thead>
<tr>
<th>Total Urinary arsenic adjusted for creatinine (µg As /g Cr)</th>
<th>Case Urine Samples (N=153)</th>
<th>Control Urine Samples (N=296)</th>
<th>Crude OR</th>
<th>95% CI</th>
<th>Adjusted OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-26</td>
<td>37</td>
<td>24%</td>
<td>86</td>
<td>29%</td>
<td>1.00</td>
<td>Referent</td>
</tr>
<tr>
<td>27-61</td>
<td>45</td>
<td>25%</td>
<td>69</td>
<td>23%</td>
<td>1.52</td>
<td>0.89, 2.60</td>
</tr>
<tr>
<td>62-135</td>
<td>33</td>
<td>22%</td>
<td>71</td>
<td>24%</td>
<td>1.08</td>
<td>0.61, 1.90</td>
</tr>
<tr>
<td>136-1998</td>
<td>38</td>
<td>25%</td>
<td>70</td>
<td>24%</td>
<td>1.26</td>
<td>0.73, 2.19</td>
</tr>
</tbody>
</table>

* Odds ratio were adjusted for weight for height (z-score less than -2 SDs and z-score greater or equal to -2 SDs), breastfeeding in the prior week (exclusive, mixed, none), paternal education, and number of people living in the household (log transformed)
Study Procedures

Case Enrollment

Arrives to icddrb Hospital

Hospital Screening For Eligibility

Hospital Timepoint

Hospital Clinical Assessment & Specimen Collection

Convalescent Timepoint

30 Day Hospital Follow-up & Specimen Collection
### Results

**Table 3B.** Crude and Adjusted Odds Ratios of Pneumonia Cases (Severe and Very Severe) for Case **(Convalescent Timepoint)** and Control Urine Samples*

<table>
<thead>
<tr>
<th>Total Urinary arsenic adjusted for creatinine (µg As/g Cr)</th>
<th>Case Convalescent Urine Samples (N=153)</th>
<th>Control Urine Samples (N=296)</th>
<th>Crude OR</th>
<th>95% CI</th>
<th>Adjusted OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-26</td>
<td>No. 24 16%</td>
<td>No. 86 29%</td>
<td>1.00</td>
<td>Referent</td>
<td>1.00</td>
<td>Referent</td>
</tr>
<tr>
<td>27-61</td>
<td>37 24%</td>
<td>69 23%</td>
<td>1.92</td>
<td>1.05, 3.51</td>
<td>2.17</td>
<td>1.14, 4.14</td>
</tr>
<tr>
<td>62-135</td>
<td>44 29%</td>
<td>71 24%</td>
<td>2.22</td>
<td>1.23, 4.00</td>
<td>2.72</td>
<td>1.42, 5.21</td>
</tr>
<tr>
<td>136-1998</td>
<td>48 31%</td>
<td>70 24%</td>
<td>2.46</td>
<td>1.37, 4.40</td>
<td>2.95</td>
<td>1.52, 5.71</td>
</tr>
</tbody>
</table>

* Odds ratio were adjusted for weight for height (z-score less than -2 SDs and z-score greater or equal to -2 SDs), breastfeeding in the prior week (exclusive, mixed, none), paternal education, and number of people living in the household (log transformed)
Discussion

Why was there only a significant association found between the case convalescent timepoint and control urine samples?
Discussion

*\( p \)-value <0.05, case hospital and convalescent timepoints compared using a paired sample t-test
Potential Explanation

If case children reduced their intake of their usual arsenic contaminated water source during their time of illness

- More breastfeeding
- Consumption of low arsenic water during hospitalization

*\(p\)-value < 0.05, case hospital and convalescent timepoints compared using a paired sample t-test
Breast-feeding Protects against Arsenic Exposure in Bangladeshi Infants

Britta Fängström,1 Sophie Moore,2 Barbro Nermell,1 Linda Kuenstl,3 Walter Goessler,3 Margaretha Grandér,1 Iqbal Kabir,4 Brita Palm,1 Shams El Arifeen,4 and Marie Vahter1

Table 2. Concentrations of arsenic in infant urine at 3 month of age, breast milk, saliva, and blood, as well as maternal urine (GW8 and GW30).

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>Mean</th>
<th>Median</th>
<th>10th–90th</th>
<th>Min–Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant urine, 3 months (μg/L)b</td>
<td>98</td>
<td>22</td>
<td>1.2</td>
<td>0.27–8.3</td>
<td>0.10–1,520</td>
</tr>
<tr>
<td>Breast milk, 2–3 months pp (μg/kg)</td>
<td>79</td>
<td>1.8</td>
<td>1.0</td>
<td>0.38–4.3</td>
<td>0.25–19</td>
</tr>
<tr>
<td>Saliva, 3 months pp (μg/kg)</td>
<td>98</td>
<td>2.5</td>
<td>1.3</td>
<td>0.69–6.3</td>
<td>0.51–17</td>
</tr>
</tbody>
</table>

For evaluation of changes over time

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>Mean</th>
<th>Median</th>
<th>10th–90th</th>
<th>Min–Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythrocytes, GW14 (μg/kg)</td>
<td>13</td>
<td>13</td>
<td>9.2</td>
<td>2.6–28</td>
<td>2.3–39</td>
</tr>
<tr>
<td>Erythrocytes, 6 months pp (μg/kg)</td>
<td>38</td>
<td>13</td>
<td>5.7</td>
<td>2.8–35</td>
<td>1.8–41</td>
</tr>
<tr>
<td>Urine, GW8 (μg/L)b</td>
<td>97</td>
<td>142</td>
<td>49</td>
<td>22–434</td>
<td>12–810</td>
</tr>
<tr>
<td>Urine, GW30 (μg/L)b</td>
<td>91</td>
<td>167</td>
<td>67</td>
<td>21–550</td>
<td>10–1,130</td>
</tr>
</tbody>
</table>

Abbreviations: Max, maximum; Min, minimum; pp, postpartum. 10th and 90th are percentiles.

*Adjusted to average SG of 1.003 g/mL. bAdjusted to average SG of 1.012 g/mL.

Reference: Fängström et al. 2008
Table 1. Characteristics of the Study Population (Cont.)

<table>
<thead>
<tr>
<th>Breastfed in the prior week</th>
<th>Cases</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Exclusive</td>
<td>22%</td>
<td>33</td>
</tr>
<tr>
<td>Mixed</td>
<td>58%</td>
<td>89</td>
</tr>
<tr>
<td>None</td>
<td>20%</td>
<td>30</td>
</tr>
</tbody>
</table>

* Control and cases compared using a two sample t-test for continuous variables and chi-square test for categorical variables

80% of Case Children were Breastfed in the Prior Week
Potential Explanation

Urinary arsenic is only a reliable measure of arsenic exposure if the source of drinking water remains constant

- If case children reduced their intake of their usual arsenic contaminated water source during their time of illness their urinary arsenic concentration could potentially decrease

Potential Explanation

Convalescent urine sample was likely a better reflection of the case child’s chronic arsenic exposure
  • Urine collected after child’s illness once the child resumed to their normal drinking water practices
Conclusion

We observed an significant association between severe and very severe pneumonia and creatinine-adjusted urinary arsenic concentrations when convalescent timepoint case and control urines were compared in children 1 – 59 months of age in rural Bangladesh.
Study Limitations

- Case control study
- Lack of information on arsenic exposure histories
- Focus on only on severe and very severe pneumonia cases
- Facility based surveillance only
Strengths

• First study to assess the association between childhood arsenic exposure and pneumonia
• Physician diagnosed severe and very severe pneumonia using WHO definition
• Use of urinary arsenic allowed for the detection of both water and dietary contributions to arsenic exposure
Future Studies

- Evaluations of markers of immune function by arsenic exposure categories
  - Percentage of CD4 T cells and IL-2 secretion levels
- Prospective evaluations of the impacts of arsenic exposure and pneumonia in pediatric populations using physician diagnosed illness
- Interventions to reduced arsenic exposure in susceptible pediatric populations
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• Al Fazal Khan
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