Master thesis:

Paediatric pneumonia in Uzbekistan – treatment and risk factors

Sandra Jernmark

Gothenburg, Sweden 2013
Paediatric pneumonia in Uzbekistan – treatment and risk factors

Master thesis in Medicine

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Abstract

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Background & Purpose:

One point two million children under five years die from pneumonia every year. Mortality is ten times higher in developing countries (like Uzbekistan) than in developed countries, due to risk factors connected to low socioeconomic status. The aim of this study was to investigate the prevalence of risk factors among pediatric pneumonia patients in Uzbekistan and to see how pediatric pneumonia patients are treated.

Materials & Methods:

A questionnaire-based prospective study was conducted at Tashkent Medical Pediatric Institute, First and Fifth hospitals in Tashkent, Uzbekistan. We included 99 children between 3-141 months old from February – April 2013. Information was collected from the questionnaire, medical records and statements from a clinician.

Results:

Crowding and indoor air pollution at home was reported for 49 % and 29 % children with pneumonia, respectively. Self-reported rickets was present in 8/77 patients, and severe pneumonia was significantly more common among these children. Metronidazol was used to a great extent. Rigid bronchoscopy was commonly used for both treatment (lavage with antibiotics and antiseptics) and diagnosis.
Discussion & Conclusion:

Many risk factors connected to low socioeconomic status were present among the patients included in the study, but also the easily preventable factor vitamin D deficiency. Another major finding was that even for one of the most common diseases in childhood in the world, treatment may be very different: rigid bronchoscopy for treatment and diagnosis is not recommended in any guidelines for treatment of pediatric pneumonia. The same is true for metronidazole, which was commonly added in pneumonia treatment, although this agent is not efficient against any of the main respiratory pathogens.
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Introduction

Pneumonia epidemiology – worldwide

Every year, 1.2 million children below the age of five years die from pneumonia, which is more than malaria, AIDS and measles combined. Pneumonia accounts for 19 % of all deaths in children under five years old [1]. It is the leading causes of death among children under five years old, together with diarrhea[2]. The incidence of pneumonia among children is at least ten times higher in developing countries compared to industrialized states[1]. During the year 2000 about 156 million new cases of clinical pneumonia occurred in the world, more than 95 % of all of them occurred in developing countries[3]. In developed countries the incidence of community-acquired pneumonia is 0.026 per child-year, whereas in developing countries the incidence is 0.280 [2].

United Nation (UN):s fourth millennium goal is to reduce the under-five mortality rate by two thirds between 1990 and 2015 [4]. In the USA the mortality has decreased with 97 % from the year 1939-1996, probably mainly due to antibiotics, vaccination and medical insurance, to a greater extent, for children [2]. Less crowding and better nutritional status probably contributed.

Etiology

Pneumonia is a parenchymal inflammation of the lungs, which can be caused by bacteria, viruses and fungi. The three major bacterial causes of pneumonia that lead to hospitalization and mortality among children under five years old in developing countries are *Haemophilus influenzae* type b (Hib), *Streptococcus pneumoniae* and *Staphylococcus aureus*. Etiology varies with age and concomitant diseases[2].
**Symptoms and Diagnosis**

Common symptoms and findings among children with pneumonia are (in descending order): fever, cough, rhinorrhea, dyspnea, lethargy, vomiting, poor appetite, headache etc.[5]. The most consistent clinical manifestation is tachypnea, which is also correlated to severity, and it is therefore recommended as a diagnostic indicator [2]. WHO has created age adjusted thresholds in respiratory rate as a guideline (see table 1). The examiner also observes other common clinical manifestations, such as the respiratory effort and examines the oxygen saturation with a pulse oximetry if available. Other parameters and examination methods that may be used to diagnose pneumonia are: chest radiography, complete blood cell count, auscultation with stethoscope, cultures from mucus and serology[2].

<table>
<thead>
<tr>
<th>Age</th>
<th>Respiratory rate/minute</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2 months</td>
<td>≥60</td>
</tr>
<tr>
<td>2-11 months</td>
<td>≥50</td>
</tr>
<tr>
<td>12-59 months</td>
<td>≥40</td>
</tr>
<tr>
<td>&gt;5 years</td>
<td>≥30</td>
</tr>
</tbody>
</table>

**Table 1**: Age-specific definitions of tachypnea by the WHO[6].

**Risk factors**

According to WHO the definite risk factors for getting pneumonia as a child is malnutrition, birth weight below 2500 g, not fully breastfed during the first four months, non-vaccination of measles the first year, indoor air pollution (such as from heating and cooking with wood or dung) and more than 5 people living together. Likely risk factors are: parental smoking, if the mother is an inexperienced caregiver, zinc deficiency and concomitant diseases (e.g. asthma, heart disease, diarrhea). Possible risk factors are: day-care attendance, mother’s education, high humidity, cold air, vitamin A deficiency and outdoor air pollution[3].
Breast feeding is recommended exclusively up to six months of age, and then continued up to two years of age or more[7].

Vitamin D has been shown in recent studies to have a connection to infectious diseases, especially pneumonia[8]. Children with severe pneumonia have been shown to have a higher prevalence of Vitamin D deficiency in some settings [9].

**Treatment**

Pneumonia should in most cases be treated with antibiotics, but only around 30% of all children with pneumonia worldwide are estimated to receive the antibiotics needed. It can be given at a health care center by trained personnel or at a hospital. Hospitalization only is recommended for children with severe pneumonia or children younger than two months[2], table 2 shows other factors suggesting need for hospitalization.

<table>
<thead>
<tr>
<th>Factors Suggesting Need for Hospitalization of Children with Pneumonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sickle cell anemia with acute chest syndrome</td>
</tr>
<tr>
<td>Multiple lobe involvement</td>
</tr>
<tr>
<td>Immunocompromised state</td>
</tr>
<tr>
<td>Toxic appearance</td>
</tr>
<tr>
<td>Severe respiratory distress</td>
</tr>
<tr>
<td>Requirement for supplemental oxygen</td>
</tr>
<tr>
<td>Dehydration</td>
</tr>
<tr>
<td>Vomiting</td>
</tr>
<tr>
<td>No response to appropriate oral antibiotic therapy</td>
</tr>
<tr>
<td>Noncompliant parents</td>
</tr>
</tbody>
</table>

**Table 2** factors for hospitalization [2].

The important initial treatment is respiratory support to the children with respiratory distress, hypercapnea and/or hypoxemia with higher concentration of oxygen, CPAP (continuous positive air pressure) or intubation[2].
Recommendations for antibiotic treatment are changing due to resistance development, therefore recommendations may vary around the world [10]. The first-line antibiotic treatment against community-acquired pneumonia is high-dose penicillin or amoxicillin which covers S. pneumoniae. Most of the outpatient children diagnosed with pneumonia are treated with oral antibiotics[11]. Intravenous cephalosporins in combination with macrolides are often used in hospitalized children[12]. Alternatives are second- or third- generation cephalosporins and macrolides. Combined therapy (amoxicillin and gentamicin or cephalosporine) is commonly used as the initial treatment of newborns and young infants. Macrolides provides cover for the common bacteria and atypical agents such as Chlamydophilia, Mycoplasma and Legionella[2].

Uzbekistan

Uzbekistan is a country located in Central Asia and borders to Kazakhstan, Afghanistan, Turkmenistan, Kyrgyzstan and Tajikistan. The Great Silk Road from China to Northern Africa, and Europe went through cities like Samarkand, Khiva and Bukhara, all located in Uzbekistan. There have been many conquests of this region, by Alexander the great, Genghis Khan and Amor Timor. The Uzbek language is from the Turkish family, the culture of the region dates from the second century. By 1876, all the regions creating today’s Uzbekistan became part of Russia. The Soviet republic Uzbekistan was created by Stalin [13], and continued to be a part of the Soviet Union until 1991 when it became independent. Already before the independency was today’s president Islam Karimov in power and in 1992 was the main opposition party banned. Since then the Human Rights situation is still bad: freedom of assembly and expression are being strictly limited, many NGO’s (Non-Governmental Organizations) have closed their offices, the organization “Freedom House” (independent
observing organization[14]) ranks Uzbekistan as one of the world’s ten most oppressed countries[15].

Uzbekistan has many natural resources; they are almost self-sufficient in gas and oil, has significant amounts of zinc, uranium, tungsten, silver, gold, copper and lead. Cotton growth is the biggest agricultural income, Uzbekistan is the second-largest exporter and the fourth-largest producer of cotton in the world[16], but this industry has disadvantages. Every year all public employees are obliged to pick cotton, it has also been reported that children are working on the fields[17]. Only 10.5 percent of the land is arable naturally which has led to artificial watering taken from the two main rivers, Amu Darya and Syr Darya. These two rivers are almost the only inflow to the Aral Sea, and the sea has therefore only about 25 % of the volume during the 1960’s [18]. This has led to climate changes, depleted fishing, problems with drinking water and soil getting contaminated with salt, pesticides and fertilizers. The agriculture of cotton that was introduced during the Soviet Union period led to that Uzbekistan did not suffer from the same economic shock like other former states[16]. GDP per capita in Uzbekistan is $3,420, compared to Sweden with $42,200 [19].

**Health care system in Uzbekistan**

The health care system throughout the country is organized in the 12 viloyats (districts). In every viloyat there is one big hospital, each viloyat is divided in to 8-11 regions with a smaller hospital each. If a patient can not be taken care of in the viloyat hospitals they can be referred to the republic hospital, Tashkent Pediatric Medical Institute (TMPI)[20]. First and Fifth hospital, where this study was conducted as well, are governmental region hospitals.
Children under fifteen years old get most medical care for free. If they are hospitalized they get the medicine for free as long as the medicine needed is available, otherwise they have to go to a pharmacy and buy it[21].

Patients seeking health care at the hospital are sometimes asked if it is possible for them to buy the recommended medicine. If not, the doctor will try to find cheaper medicine that is also effective. The patient might give out-of-pocket money, just a few thousand sum (1000 sum ≈ 3 SEK [22]), out of pure heart[23].

Our main study site was TMPI, which is a national referral hospital offering highly specialized care, mainly for children under 24 months old. If further care than what can be given in other institutes is needed, the patient is referred to TMPI without a fee. The hospital does not have neither MRI nor computer tomography, but has access to it through a private hospital, where patients have to pay themselves[23]. The hospital has 265 beds divided into 15 different departments, 25 beds in the pulmonary department. In 2012 TMPI had 15 000 patients that were hospitalized and 95 000 patients in total. It is completely financed by the government[24].

Total (outpatient and admissions) number of patients on TMPI

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002</td>
<td>17-18 000</td>
</tr>
<tr>
<td>2011</td>
<td>100 000</td>
</tr>
<tr>
<td>2012</td>
<td>&gt;95 000</td>
</tr>
</tbody>
</table>

Mortality rate

<table>
<thead>
<tr>
<th>Year</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007</td>
<td>1.6%</td>
</tr>
<tr>
<td>2012</td>
<td>0.6%</td>
</tr>
</tbody>
</table>

Numbers from a presentation by superintendent Dr Mallaboevna [24]
Pneumonia in Uzbekistan

Of a total population of 29 million[25], 2.8 million were children under five years old in Uzbekistan in 2011[26]. The under-five mortality rate was 52/1,000 in Uzbekistan compared to 3/1,000 in Sweden[27]. Uzbekistan has an infant (<1 year) mortality rate at 42/1,000 [28], in 2008 the leading cause of death in Uzbekistan was pneumonia, accounting for 22 % [29].

In Uzbekistan 68 % of the children with suspected pneumonia have been estimated to see an appropriate health care provider, and only 56 % get treated with antibiotics[30]. It can be prevented by immunization against pneumococci, *Haemophilus influenzae type B* (Hib), measles and pertussis. Ninety-nine percent of the 1-year-old children in Uzbekistan are estimated to be immunized against the three latter pathogens and tuberculosis in 2010[30]. In contrast, very few children receive pneumococcal conjugate vaccine since it is not included in the general vaccination program[26].

At TMPI the Russian classification method for diagnosing pneumonia is used, see Appendix nr I. Pneumonia can be classified in many ways: according to acquisition, underlying diseases, clinical course, etiology (see table 3).

<table>
<thead>
<tr>
<th>Classification of pneumonia</th>
<th>Conditions of infection</th>
<th>Clinical course</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Community-acquired</td>
<td>- Acute</td>
<td></td>
</tr>
<tr>
<td>- Nosocomial</td>
<td>- Protracted (prolonged)</td>
<td></td>
</tr>
<tr>
<td>- Perinatal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- In immunocompromised patients</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3 Classifications of pneumonia[31].
**Aim/specific objectives**

To our knowledge, the literature provides no descriptions of risk factors and management of child pneumonia in Uzbekistan. This information can be useful when designing preventive strategies.

Which risk factors for pneumonia are present among children treated for pneumonia in Tashkent? Is there a correlation between the severity of pneumonia and some of the risk factors? What treatment is given? What examinations are performed?

The aims of this study are to study the following aspects of pneumonia:

- the epidemiology including age and sex distribution
- the prevalence (%) of prognostic factors, e.g. underlying diseases, malnutrition, environmental risk factors (smoking in household, smoke from cooking, crowding), socioeconomic factors, school attendance
- clinical symptoms including respiratory rate, oxygen saturation, heart rate, presence of retractions
- data on treatment and outcome with mortality and complications.

**Method**

This is a questionnaire-based study on children with pneumonia at mainly TMPI, but also First and Fifth hospital. Patients were included consecutively from the pulmonary ward, the polyclinic (out-hospital patient) and the emergency room in TMPI. The study was conducted from February to April 2013, and from middle of March to middle of April patients from two other hospitals in Tashkent was included, Fifth hospital and First hospital. The patients included in the study were diagnosed with pneumonia by a doctor according to the criteria
(see appendix nr I). Patients for whom the pneumonia diagnosis was changed or whose caretakers did not consent to fill out the questionnaire were excluded.

The patients themselves or a relative answered the questionnaire and approval (see appendix nr II) with assistance and interpretation of one of the clinical ordinators. Clinical data (e.g. weight, respiratory rate, treatment and the parents’ occupation) of the children was taken from the medical records of the first examination at TMPI. Local doctors were interviewed in order to investigate treatment and diagnostic routines, including questions about when and how to perform rigid bronchoscopy.

A clinical ordinator is a person who does his specialization only clinical, compared to the other specialization program which is magister and includes research.

The outcome of the patients was measured as length of stay. The mortality rate among the children included in the study was zero so therefore this variable could not be used as an outcome indicator.

The following definition for severe pneumonia was used: presence of one or more of: retractions at time of the examination (the same occasion as the questionnaire was filled out), vomiting or confusion as a symptom before coming to the hospital/polyclinic.

**Statistical methods**

All analyzes were made in IBM SPSS Statistics Version 21. The categorical data were analyzed with $\chi^2$ if no cells had expected count less than five, in such cases we used Fisher’s Exact Test. The continuous data were analyzed with one-way ANOVA by comparing means. Tables were made in Microsoft Excel 2007.
**Ethics**

The study was approved by the sitting committee of TMPI, Tashkent, Uzbekistan and by superintendent at First and Fifth hospital. All patients or caretakers got written and oral information that participation in the study was voluntary, that they had the right to withdraw their participation at any time during the study and without any further explanation, and that the medical treatment would not be affected whether they were included in the study or not. Dr Nuriddin Aslamoovitj approved usage of information from the medical records without the patients approval. The patients included did not receive any compensation. No individuals can be identified in the data.

**Results**

**Demographics**

We were able to include 99 patients in the study, 55 boys and 30 girls, age 3-141 months. 86 of them filled out the questionnaire and for the remaining 13, information taken from the medical records. The patients were collected from TMPI hospital (74), TMPI polyclinic (4), First hospital (11) and Fifth hospital (7).
Age distribution is shown in figure 1. Boys are younger than girls, although not significant:

![Age distribution between the sexes.](image)

Figure 1, age distribution between the sexes.
Fifty-five percent of the patients (n=85) were from Tashkent region, and the rest from other regions with an even distribution. 72 % were from urban areas and 28 % from rural areas.

Altogether 29 % of the children lived in homes where food was cocked over an open fire without a chimney. Sixty-three percent of the mothers were housewives.

In more than half of the cases, the patient had first visited a polyclinical hospital (see table 4).

<table>
<thead>
<tr>
<th>Seeking health care (n=86)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary health care center</td>
<td>14</td>
</tr>
<tr>
<td>Polyclinical hospital</td>
<td>57</td>
</tr>
<tr>
<td>Private clinic</td>
<td>5</td>
</tr>
<tr>
<td>Rural health care center</td>
<td>13</td>
</tr>
<tr>
<td>Specialist center</td>
<td>7</td>
</tr>
<tr>
<td>Hospital</td>
<td>5</td>
</tr>
</tbody>
</table>

**Table 4** First contact with health care
The majority of the children was or had been breast fed (see table 5).

<table>
<thead>
<tr>
<th>Have been breast fed?</th>
<th>Percent (n=86)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>6%</td>
</tr>
<tr>
<td>Yes</td>
<td>69%</td>
</tr>
<tr>
<td>Yes, still is</td>
<td>25%</td>
</tr>
</tbody>
</table>

Table 5 Breast feeding

Patients with severe pneumonia were 23 out of 84 and in table 6 and 7 we compare the prevalence of a risk factor/symptom/finding among patients with severe and mild pneumonia.

\[
\text{Risk factor} / \text{total nr of severe or mild pneumonia} \times 100 = \%
\]

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>severe pneumonia %</th>
<th>mild pneumonia %</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age: 0-35 months (n=50)</td>
<td>70</td>
<td>56</td>
<td>0.250</td>
</tr>
<tr>
<td>36-141 months (n=34)</td>
<td>30</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>Sex: girl (n=29)</td>
<td>35</td>
<td>35</td>
<td>0.985</td>
</tr>
<tr>
<td>boy (n=54)</td>
<td>65</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>Origin: urban (n=61)</td>
<td>65</td>
<td>77</td>
<td>0.290</td>
</tr>
<tr>
<td>Crowded household (=84)</td>
<td>52</td>
<td>46</td>
<td>0.608</td>
</tr>
<tr>
<td>Open fire indoor (n=24)</td>
<td>39</td>
<td>25</td>
<td>0.188</td>
</tr>
<tr>
<td>Other lung disease (n=7)</td>
<td>5</td>
<td>10</td>
<td>0.667</td>
</tr>
<tr>
<td>No pneumococcvacc. (n=35)</td>
<td>44</td>
<td>41</td>
<td>0.667</td>
</tr>
<tr>
<td>No Hib type B vaccine (n=18)</td>
<td>22</td>
<td>21</td>
<td>0.945</td>
</tr>
<tr>
<td>No measles vaccine (n=8)</td>
<td>4</td>
<td>12</td>
<td>0.433</td>
</tr>
<tr>
<td>Rickets (n=7)</td>
<td>26</td>
<td>4</td>
<td>0.010</td>
</tr>
<tr>
<td>Similar symptoms in family (n=28)</td>
<td>37</td>
<td>33</td>
<td>1.000</td>
</tr>
<tr>
<td>Treated for similar disease before (n=47)</td>
<td>65</td>
<td>53</td>
<td>0.495</td>
</tr>
<tr>
<td>Similar disease last month (n=36)</td>
<td>43</td>
<td>43</td>
<td>0.740</td>
</tr>
<tr>
<td>Underweight (n=30)</td>
<td>40</td>
<td>48</td>
<td>0.557</td>
</tr>
<tr>
<td>Family members smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 (n=48)</td>
<td>61</td>
<td>58</td>
<td>1.000</td>
</tr>
<tr>
<td>1 (n=30)</td>
<td>35</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>2 (n=6)</td>
<td>17</td>
<td>83</td>
<td></td>
</tr>
</tbody>
</table>

Table 6 Risk factors
Table 7 Clinical observations

<table>
<thead>
<tr>
<th>Symptom/finding</th>
<th>Severe pneumonia %</th>
<th>Mild Pneumonia %</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever before hosp. (n=53)</td>
<td>70</td>
<td>61</td>
<td>0.451</td>
</tr>
<tr>
<td>Cough before hosp. (n=74)</td>
<td>91</td>
<td>87</td>
<td>0.347</td>
</tr>
<tr>
<td>Chest pain before hosp. (n=8)</td>
<td>13</td>
<td>8</td>
<td>0.678</td>
</tr>
<tr>
<td>Difficult breathing before hosp. (n=32)</td>
<td>44</td>
<td>36</td>
<td>0.533</td>
</tr>
<tr>
<td>Rapid breathing before hosp. (n=27)</td>
<td>44</td>
<td>28</td>
<td>0.172</td>
</tr>
<tr>
<td>Runny nose before hosp. (n=39)</td>
<td>57</td>
<td>43</td>
<td>0.255</td>
</tr>
<tr>
<td>Nausea before hosp. (n=14)</td>
<td>39</td>
<td>8</td>
<td>0.002</td>
</tr>
<tr>
<td>Headache before hosp. (n=16)</td>
<td>39</td>
<td>12</td>
<td>0.10</td>
</tr>
<tr>
<td>Muscular pain before hosp. (n=10)</td>
<td>26</td>
<td>7</td>
<td>0.023</td>
</tr>
<tr>
<td>Tachycardia (n=11)</td>
<td>9</td>
<td>17</td>
<td>0.488</td>
</tr>
<tr>
<td>Chest deformation (n=13)</td>
<td>16</td>
<td>18</td>
<td>1.000</td>
</tr>
<tr>
<td>Hyperventilation (n=11)</td>
<td>17</td>
<td>13</td>
<td>0.724</td>
</tr>
</tbody>
</table>

There was no correlation between severe pneumonia and the risk factors: not being breast fed, not getting BCG vaccine, family member with tuberculosis, diagnosed with HIV, heart disease, kidney disease, measles and preterm birth > 3 weeks (data not shown).

Significantly (p=0.009) younger children were treated at Fifth and First hospital compared to the older children at TMPI. There was no correlation between other diseases, vaccination, clinical signs and location of hospitalization.

Observations at TMPI

The diagnosis were distributed like this: clinical course: acute/prolonged 65/31 and condition of infection: community-acquired/nosocomial 90/4 (see table 2 for diagnosis classifications).

Number of days treated at the hospital was 9.8 in mean and 9 in median, out of 52 patients.

Five percent of the patients had retractions present during the time of examination, which is one of the criteria for severe pneumonia. Figure 2 shows the distribution of severe pneumonia (%) within the age groups in months.
**Treatment**

All patients were treated with antibiotics. The mean duration was 8 days with 3 day standard deviation.

The distribution of the antibiotic treatment is shown in table 8.

<table>
<thead>
<tr>
<th>Antibiotic group</th>
<th>Percent (n=94)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cephalosporine + Metronidazol</td>
<td>32</td>
</tr>
<tr>
<td>Cephalosporine</td>
<td>51</td>
</tr>
<tr>
<td>Aminoglycoside</td>
<td>13</td>
</tr>
<tr>
<td>Cephalosporine + Aminoglycoside</td>
<td>2</td>
</tr>
<tr>
<td>Penicilline + Cephalosporine + Aminoglycoside</td>
<td>1</td>
</tr>
<tr>
<td>Cephalosporine + Aminoglycoside + Amoxicillin</td>
<td>1</td>
</tr>
</tbody>
</table>

**Table 8** Antibiotic treatment.

Most patients had been treated with penicillin without success before arrival at TMPI. Cephalosporins were given alone or in combinations, in 87 percent (see table 8). Patients with recurrent pneumonia received Ceftriaxon or Cefazolin. Gentamicin was given to patients with recurrent cough. If there was no observed improvement with the first administered antibiotic...
treatment, metronidazole was added in 32 percent of the cases. Cefepim was given to the most severe cases[32]. Cultures from bronchoscopy lavage were not done by routinely, although they were done to a great extent it was not guiding for the antimicrobial treatment.

The patients got antibiotics free from the pharmacy at the hospital for three days, and thereafter they had to buy it themselves. If the patients were not able to buy medicine, the hospital provided them with antibiotics, but the majority of the patients could afford the medicine. When the hospital pharmacy could not provide the patients with the antibiotic needed, the patients search it in another pharmacy. There were many pharmacies close and the doctors did not consider it being a problem. The patients got plastic gloves, needles, potassium chloride, sodium chloride and Theophylline for free at the hospital pharmacy[32].

No patients were treated with continuous positive air-pressure or respirator. One patient out of 82 patients was treated with oxygen. 83 % of the patients were treated with inhalations.

The distribution of the inhalators given as a treatment is shown in table 9.

<table>
<thead>
<tr>
<th>Types of inhalators</th>
<th>Percent (n=74)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodiumhydrocarbonate</td>
<td>50</td>
</tr>
<tr>
<td>Magnesiumsulfate</td>
<td>72</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>27</td>
</tr>
</tbody>
</table>

Table 9 Inhalations.

**Bronchoscopy**

25 patients had a rigid bronchoscopy performed on them and 69 did not. There were a difference in mean days of hospitalization between the patients who had a rigid bronchoscopy performed and the ones who did not. Indications for rigid bronchoscopy: prolonged
pneumonia, bronchiectasis and foreign body, signs from x-ray, CT and auscultation. Bronchoscopy was performed in all ages, but it was seldom used for only diagnosis, usually curative as well: the clinician performing the bronchoscopy always washed the airways with antiseptics and the same antibiotic as the patient received as a treatment. The interviewed bronchoscopist has not had any complications in 2-3 years[33].

The patients who were treated with bronchoscopy seemed to have a longer mean length of hospitalization than the ones who did not (10.6 and 9.4 days respectively, not significant). In 27 % of the patients was bronchoscopy a part of the treatment, with purulent endobronchitis as a finding. “Purulent endobronchitis” was found as a complication to pneumonia, in all patients who did a bronchoscopy. There were more younger children who had a bronchoscopy performed on them (see figure 3). According to an experienced clinician was bronchoscopy only performed once on a child, in rare cases it was performed twice on the same child. Thirty to forty percent of the children diagnosed with pneumonia did not need a bronchoscopy, the remaining would get well in 20 days without bronchoscopy and in 10 days with bronchoscopy, claimed by a clinical practitioner[33]. The child was put to sleep with diazepam and ketamine (if the child has a heart disease fentanyl was used instead of ketamine). The lower limit for oxygen saturation was 80 % during the bronchoscopy [33]. The bronchoscopy was performed with a rigid bronchoscope. There was only a flexible bronchoscope available for adults. Figure 3 shows the age distribution of children who had a rigid bronchoscopy performed and the ones who did not.
Figure 3 Age distribution among bronchoscopies.

Outcome
Mortality was zero in our study group which is in line with the mortality rate 0.6% in 2012 [24]. The time of hospitalization was 9.8 days in mean (minimum 2 days and maximum 19 days).

Discussion

Main findings
There were 25/94 patients who had a bronchoscopy performed on them, with a rigid bronchoscope. In this study population no difference in length of hospitalization depending on bronchoscopy was seen. This may be that the children who had a bronchoscopy performed were more ill in general, or that they were hospitalized due to the bronchoscopy. We found that 34% of the younger (0-35 months) children vs. 17% of the older (≥36 months) children had a bronchoscopy made on them. It might be that the younger children have more
complications or more frequently aspiration pneumonia. To our knowledge there are no guidelines today that suggest rigid bronchoscopy as a part of the treatment against pneumonia. No local international guidelines, to our knowledge, recommend local washing of the lungs with antiseptics and antibiotics.

Patients with self-reported rickets, according to the answerer, had a significantly higher incidence of severe pneumonia than the ones who did not have self-reported rickets. Another study was conducted on a sub-group of our patient population, focusing on the presence of signs and symptoms of severe vitamin D deficiency among children with pneumonia. That study did not find such a correlation, probably because that study population was smaller [34]. That vitamin D deficiency seems to be common in Uzbekistan is underlined by an article from 2008 conducted in Samarkand, where 78 % of 474 infants had vitamin D deficiency, which can lead to rickets [35]. That study was conducted in a different region, on a primary health care center and on younger patients, and can therefore not be used as a control-group to this study. Two other articles from other parts of the world have shown a higher prevalence of rickets among children with pneumonia than in a control-group [9, 36]. It is likely to believe that high prevalence of vitamin D deficiency contributes to the high pneumonia incidence in Uzbekistan, but it cannot be proven since we did not have a control group.

When we compare the group by severe pneumonia and age we can see that is it a trend that severe pneumonia is more common among younger children (see figure 3) O. B. Oleksiuk et al found that pneumonia is more common among younger children (see figure 2) [37]. Children’s immune system develops with age and they don’t have as good resources to handle an infection as an older child.
Symptoms like nausea, muscular pain and headache also gives a significantly higher risk of getting severe pneumonia according to our data. This might be because the symptoms defining severe pneumonia are interrelated with the mentioned ones and if one symptom is present it is more likely that the patient has more/other symptoms. And it might also be hard to decide whether a small is child is suffering some if these symptoms.

We found no significant difference in severe pneumonia among vaccinated against *S. pneumoniae*, Hib and tuberculosis and non-vaccinated (see table 6). More children than expected were reported vaccinated against *S. pneumoniae* is not included in the national vaccination program[26], and since the vaccine is expensive it is likely that the answers on this question were incorrect or the patient went to a private clinic to get the vaccination.

Physiotherapy was used as an important part of the treatment, the patients got inhalations twice a day at the physiotherapy department. 97% of the patients from the pulmonary ward at TPMI received treatment with inhalations. Whether or not a child got inhalations did not depend on severity or if they had obstructivity or not. No children got inhalations with beta-2 stimulators. The most common substances used (sodiumhydrocarbonate and magnesiumsulfate) are not part of any international recommedations. A Cochrane report from 2005 concluded that nebulized inhaled magnesium sulfate in addition to beta2-agonist in the treatment of acute asthma exacerbations appeared to have some benefits, but there is data on pneumonia treatment[38]. Long-acting glucocorticoids are commonly used in asthma treatment, but there are no guidelines suggesting nebulized hydrocortisone as a part of pneumonia treatment. To our knowledge, there are no general guidelines for treating pneumonia with inhalations, unless obstructivity is problem. It would be of great importance
to do double-blind randomized controlled studies to evaluate the effect of the inhalation therapies that are commonly used as part of pneumonia treatment in Uzbekistan.

The outcome was supposed to be measured by mortality, but due to no mortality rate the outcome may be measured in the frequency of complications, by treatment with bronchoscopy (25%) or number of mild vs. severe (23%) pneumonia and length of stay at the hospital (9.8 days in mean and 9 days in median). According to O. B. Oleksiuk et al the average length of stay at the hospital is 11.7 days for children with pneumonia[37].

This study population is by no means representative for Uzbekistan. First, the TMPI mainly receives older children. Secondly, most patients were referral patients. Many of them had received penicillin treatment without effect before being admitted. Etiology was unknown in the vast majority of cases. Although cultures were taken they were not considered to be reliable by the clinician in charge[33]. Treatment failures to penicillin can depend on many reasons: antimicrobial resistance in pneumococci, Staphylococci or Haemophilus, is an increasing problem worldwide [39-41]. Treatment failure can also be due to empyema formation, but no patient in the study had empyema.

Viruses can also cause pneumonia, and of course never respond to antibiotics, furthermore several pathogens, including mycoplasma, chlamydophilae and legionella, are never penicillin susceptible. It is remarkable that no patients got treated with macrolids, neither as a single drug, nor in combination with cephalosporine. A majority of the patients, 88% were treated with only cephalosporine or cephalosporine and metronidazole in combination. If an ethiological diagnosis could be made, using cultures and PCR against various respiratory pathogens, antimicrobial treatment could be more directed.
Risk factors such as malnutrition, indoor air-pollution, low socioeconomic status, low maternal education, poor access to care and concomitant illness were not found to be significantly associated with severe pneumonia [42]. Underweight was found in 1/3 of the patients, but it is likely to believe that underweight often was as a result of the infection rather than a preexisting risk factor, since many of the referral patients had been ill for a while before being admitted.

**Conclusions**
Many risk factors connected to low socioeconomic status were present among the patients included in the study. Another major finding was that even for one of the most common diseases in childhood in the world, treatment can be very different in different countries not only due to varying resources: rigid bronchoscopy was used frequently for treatment and diagnosis, although no guidelines recommend this for children with pneumonia. Furthermore, metronidazole was commonly used in pneumonia treatment, although this agent is not efficient against any of the main respiratory pathogens, and is therefore not recommended in any guidelines except for empyema. Probably, local clinical traditions have a major impact.

**Strengths and weaknesses**
The main weakness of our study is that we did not have a control-group, therefore all the comparisons had to be made between patients with severe and mild pneumonia. The study group is not big enough to get significance in multi variable comparisons e.g. region of origin or age with severity, other studies have had larger study groups: [43] [44] [37]. The underlying diseases are filled out by the answerer and not taken from the medical records, therefore the results based on this are not as certain.
The questionnaire was translated into the mother tongue of the answerer (both Uzbek and Russian) which decreased the language obstacles, although it would have been preferable to use the same interpreter both in contact with the patients and to read the medical records. The cultural differences towards implementing master thesis were an obstacle for collecting material. We did not have a local supervisor specialized in the subject, which would have improved the study.

The clinical signs were taken from the referral hospital and it would have been preferable to have it from the first contact with health care, it might be due to this that the patients did not present with fever. In order to get higher internal validity a homogeneous group concerning age, institute and origin would be preferable. Some of the patients have some variables missing due to lack of knowledge/information from the answerer or the doctors or misinterpretations of the questions in the questionnaire.

**Further research**

A randomized cohort-study on the use and outcome with rigid bronchoscopy on children with pneumonia is suggested because there are no researches supporting the use of rigid bronchoscopy in the treatment of pneumonia in children. Since bronchoscopy is used in a great extent and the etiology is usually unknown, would it be interesting at the same time to cultivate and perform molecular biology on samples from bronchoalveolar lavage to get the etiology and susceptible antimicrobial treatment. Another field to investigate could be the evaluate Metronidazol as a part of the treatment against pneumonia. Furthermore, a double bild randomized controlled study of the different inhalation therapies that were used would be of great interest.
A future study may compare the prevalence of risk factors connected with socioeconomic status between the different viloyats, due to different living conditions.

**Populärvetenskaplig sammanfattning på svenska**

**Lunginflammation hos barn i Uzbekistan – behandling och riskfaktorer**


Vi fann också att på detta sjukhus används rak bronkoskopi som behandling mot lunginflammation. Rak bronkoskopi är en undersökningsmetod som innebär att man går ner med ett stelt rör ett rör i luftroren till lungorna. I samband med den raka bronkoskopin sköljdes lungorna med antibiotika och bakteriedödande medel. Detta är anmärkningsvärt då rak bronkoskopi ej är rekommenderad vid bakterieorskad lunginflammation och anses vara ett stort ingrepp då det kräver att patienten är sövd. Att undersöka detta vidare för att se om bronkoskopi leder till snabbare förbättring är av yttersta intresse.
Trångboddhet, luftförroreningar inomhus och rakit (engelska sjukan) var vanligt förekommande hos en stor andel av barnen som var sjuka i lunginflammation, dessa tre utgör riskfaktorer för att få lunginflammation. Att undersöka dessa och andra riskfaktorer närmre kan vara av stort värde för att ringa in riskgrupper i fråga om regionsursprung, åldersgrupp, kön m.m. för att se på vilka förbättringar som är möjliga att genomföra.

Detta var en översiktsstudie i hur situationen ser ut för barn med pnuemoni på ett av de största sjukhusen i Uzbekistan och för att kunna gå vidare och designa studier för förebyggande åtgärder krävs grundläggande data som detta.
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Appendix I

“The criteria for diagnosis

I. Anamnesis: association with viral respiratory infection, cold-related factor.

II. Clinical:

1. Toxicity syndrome (varying degrees of severity): sleep disturbance, fatigue, weakness, or hyper-excitability, restlessness, convulsive readiness, in some cases - convulsive seizure, impaired appetite until anorexia, fever, febrile type, fever more than 5 days, marked pallor, tachycardia not corresponding to the level of fever, muffled heart sounds, decreased physiological reflexes, muscle hypotonia, dyspepsia, a drop in body weight up to exsiccosis development, enlargement of the liver.

2. Respiratory distress syndrome: dyspnea of mixed character, auxiliary muscles involved in breathing (extension of compliant sites of the chest, nasal flaring), cyanosis nasolabial triangle, worse on exertion.

3. Broncho-pulmonary syndrome: more typical localization of the one-sided pathological process in the lungs - a shortening of percussion sound corresponding over the lesions, presence of a severe, bronchial or respiratory depression in the field of lesion, gain bronchophony in a particular segment and voice tremor, fine moist rales or crepitations.

III. Paraclinic investigations:

a) Analysis of blood - leukocytosis with a left shift neutrocytosis (in young infants may be lymphocytosis), elevated erythrocyte sedimentation rate (20 mm / hour), in infants early anemia;

b) Chest X-ray - infiltrates the lung tissue of focal or segmental nature and the hilum on the affected side." [31]
Appendix II

Pneumonia among children in Tashkent, Uzbekistan

Information to patients
Dear participant,
In the study we want to examine pneumonia among children at age 0-15 years in Tashkent, Uzbekistan. We want to study risk factors, symptoms, treatment and outcome of this disease. The study is part of a collaboration between the Tashkent Pediatric Medical Institute and the Sahlgrenska Academy at the University of Gothenburg, Sweden.
If you would like to participate in the study, we will ask you to fill out a questionnaire with questions concerning the topics above. This will take approximately 10 minutes. It is of course voluntary to answer the questionnaire and you can choose not to answer a certain question without further explanation. We will perform a small physical examination, which is voluntary and only takes a few minutes. We will also look in the medical record to evaluate the diagnosis and treatment, as well as follow up on the course of the disease during the stay at the hospital.
All collected information will be handled with confidentiality. When analyzing our collected data we will not present it in a way that individual patients can be identified. We hope you want to participate, but if you choose not to participate it will not affect your treatment and care at the clinic.

Thank you for your time and interest!

Sandra Jernmark, medical student, Sahlgrenska Academy, Gothenburg University, Sweden.
Lisa Jansson, medical student, Sahlgrenska Academy, Gothenburg University, Sweden.
Supervisors:
Prof Murod Jafarov, Tashkent Pediatric Medical Institute, Tashkent, Uzbekistan
Dr Erik Backhaus, Skaraborg Hospital, Skövde, Sweden

Place and date  
Signature
Questionnaire to be filled out by parent or guardian of the child
Pneumonia among children age 0-15 years in Tashkent, Uzbekistan.

Sandra Jernmark, Lisa Jansson
Medical student, Sahlgrenska Academy, University of Gothenburg, Sweden

1. Child's age ______
Sex:
☐ girl
☐ boy

2. The questionnaire is answered by
☐ mother
☐ father
☐ I am answering myself
☐ Other, specify:___________

3. Residential area:
In what city/village do you live?
_________________________

4. Is food being cooked over open fire
without a chimney in your home?
☐ Yes
☐ No

5. Preterm delivery
☐ No
☐ Yes, specify how many weeks_____ __

6. Have you been breastfed?
☐ No
☐ Yes, specify how many months _____
☐ Do not know

7. Does any of your family members
smoke?
☐ No
☐ Yes, specify how many _____ persons

8. Do you smoke?
☐ No
☐ Yes, specify how many per day _____

9. Do you attend to school?
☐ No
☐ Yes, specify for how many years _____

10. Are you vaccinated against
Streptococcus Pneumoniae?
☐ Yes
☐ No
☐ Do not know

11. Are you vaccinated against
Haemophilus Influenzae type b, Hib?
☐ Yes
☐ No
☐ Do not know

12. Are you vaccinated against
measles?
☐ Yes
☐ No
☐ Do not know

13. Are you vaccinated against
tuberculosis (BCG)?
☐ Yes
☐ No

14. Does anyone in your family have
tuberculosis?
☐ Yes
☐ No

15. Are you diagnosed HIV positive?
☐ Yes
☐ No
☐ I have not been tested for HIV

16. Number of household members in your home: _____ persons
17. Number of children in your household: _____persons
18. Number of rooms in your home: _____
19. Number of household members sharing bedroom with your child: _____ persons
20. Do you have or have you had any of the following diseases?
   a. Lung tuberculosis   □ Yes □ No
   b. Asthma           □ Yes □ No
   c. Other lung disease □ Yes □ No If yes, please specify
   d. Cancer           □ Yes □ No If yes, please specify
   e. Heart disease    □ Yes □ No If yes, please specify
   f. Diabetes         □ Yes □ No If yes, please specify
   g. Kidney disease   □ Yes □ No If yes, please specify
   h. Measles          □ Yes □ No If yes, when
   i. Rickets          □ Yes □ No

21. Where did you first seek health care?
   □ Primary Health Care
   □ Polyclinic hospital
   □ Private hospital
   □ Rural health care center
   □ Specialist center
   □ Other, please specify

22. What transport did you use to get to this hospital?
   □ public transport
   □ car
   □ taxi
   □ ambulance
   □ other, please specify ______

23. What symptoms did you have when you came to the hospital?
   a. □ Fever, if yes how many days: ______
   b. □ Coughing
   If you were coughing, was it:
   c. □ Dry
   d. □ Wet
   e. □ Chest pain
   f. □ Difficulties breathing
   g. □ Rapid breathing
   h. □ Rinny nose

24. In the past month, has anyone in your family had similar symptoms as you?
   □ Yes
   □ No
   □ Do not know

25. Have you been treated for a similar disease before?
   □ Yes, please state when: __________________________
   □ No
   □ Do not know

26. Have you had any similar disease the last months?
   □ Yes, please state how many times ______
   □ No
   □ Do not know

Thank you for your participation!
At the time for examination, date _____
1. Weight _____
2. Length _____
3. Oxygen saturation _____
4. Temperature (°C) _____
5. Respiratory rate _____
6. Heart rate _____
7. Retractions ______
8. Treatment the patient have had for the pneumonia
   Antibiotics
   □ Yes, please specify what kind _____________________________
   □ No

9. Fluids
   □ Yes, please specify how much (duration, quantity) __________
   □ No

10. Oxygen
   □ Yes, please specify how much
       (duration, quantity) _______
   □ No

11. Inhalators
   □ Yes, please specify what kind _______
   □ No

12. CPAP (continuous positive airway pressure) or respiratory treatment
   □ Yes, please specify how much and
       what form (duration, quantity) _______
   □ No

13. Bronchoscopy performed
   □ Yes, please specify result _______
   □ No

14. Parent’s professions
    mother ____________
    father ____________

15. Clinical diagnosis
    □ Acute pneumonia
    □ Protracted (prolonged) pneumonia

16. Conditions of infection
    □ Community-acquired
    □ Nosocomial
    □ Perinatal transmitted
    □ In immunocompromised patients

17. Time at the hospital
    Date of arrival___________
    Date of discharge________

18. Chest deformation?
    □ Yes
       □ Rickets
       Due to
       □ Congenital
    □ No
Temporary appendix about vitamin D

Date of birth_______
Birth weight__________g

Number of inhabitants in residential village/city__________
Name of viloyat_________

How many times did you have a cold the last 6 months?

Have you gotten information about vitamin D supplementation?
☐ yes
☐ no
If yes, please state from where__________

Has your child taken Vitamin D supplementation?
☐ yes
☐ no
If yes, from ___months of age to _______months of age

Have you (mother) taken vitamin D?
☐ yes
☐ no
If yes,
☐ during pregnancy
☐ after pregnancy

How much time is your child spending outdoors?
☐ never outdoors
☐ 1 h/week
☐ 1–3h/week
☐ 4–6h/week
☐ 1–3h/day
☐ >3 h/day

Thank you for your participation!

To be filled out by examinators:

Clinical signs of hypovitaminosis?
☐ yes
☐ no
Please state which__________________
_______________________________________

Clinical signs of rickets?
☐ yes
☐ no
Please state which__________________
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