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**Influenza related pneumonia in children under five years old in Indonesia :
An analysis of the risk factors**

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Abstract

Background : Pneumonia is more commonly among children under five years old and caused by several risk factors. Pneumonia causes 1.9 – 2.2 million children death worldwide every year, in which 1.3 million (81%) generally occurs in first 2 years of life. Seventy two percent of pneumonia occurs in children under five years old in 15 countries. Indonesia was the 7th highest in the world. The prevalence of pneumonia in Indonesia was 18.5/1000 population and only 1.6/1000 received treatment. Objective of the study is to elaborate the risk factors of the influenza related pneumonia in children under five years old.

Method : The pneumonia control program in Ministry of Health focuses on early detection and treatment for bacterial pneumonia in community. Severe acute respiratory infection (SARI) can develop fatal pneumonia. We collected data from the pneumonia surveillance database in the Acute Respiratory Infection sub directorate.

Results : Influenza related pneumonia was 13% of acute lower respiratory infection in pediatric. The number of children under five years old death estimation was 28,000-115,000 and 99% happened in developing countries.

Conclusion : In Indonesia, proportion of influenza from SARI surveillance was 12% and mainly in children under five years old (36%). Pneumonia was 18% of SARI cases with positive influenza. The effect of Influenza become pneumonia remain unclear.

Key words: Pneumonia, Influenza, SARI, children

Abstrak

Latar Belakang : Pneumonia lebih sering terjadi pada anak-anak di bawah lima tahun dan disebabkan oleh beberapa faktor risiko. Pneumonia menyebabkan 1,9 - 2,2 juta kematian anak-anak di seluruh dunia setiap tahun, di mana 1,3 juta (81%) umumnya terjadi pada 2 tahun pertama kehidupan. Tujuh puluh dua persen pneumonia terjadi pada anak-anak di bawah lima tahun di 15 negara. Indonesia adalah yang tertinggi ke-7 di dunia. Prevalensi pneumonia di Indonesia adalah 18,5 / 1000 populasi dan hanya 1,6 / 1000 yang menerima pengobatan. Tujuan dari penelitian ini adalah untuk menguraikan faktor risiko pneumonia terkait influenza pada anak-anak di bawah lima tahun.

Metode: Program pengendalian pneumonia di Kementerian Kesehatan berfokus pada deteksi dini dan pengobatan untuk pneumonia bakteri di masyarakat. Infeksi pernapasan akut yang berat (SARI) dapat menyebabkan pneumonia yang fatal. Kami mengumpulkan data dari database pengintaian pneumonia di subdirektorat Infeksi Saluran Pernapasan Akut.

Hasil : Influenza terkait pneumonia adalah 13% dari infeksi saluran pernapasan akut bawah pada anak. Jumlah perkiraan kematian balita adalah 28.000-115.000 dan 99% terjadi di negara berkembang.

Kesimpulan : Di Indonesia, proporsi influenza dari surveilans SARI adalah 12% dan terutama pada anak-anak di bawah lima tahun (36%). Pneumonia adalah 18% kasus SARI dengan influenza positif. Efek influenza menjadi pneumonia tetap tidak jelas.

Kata kunci : Pneumonia, Influenza, SARI, balita

INTRODUCTION

Severe acute respiratory infection (SARI) can develop progressive pneumonia in few hours and cause fatal pneumonia in children under five years old. Pneumonia remains the most cause of death in children under five years old worldwide. Of 5.9 million children death globally, pneumonia was 16%. 72% of pneumonia has happened in 15 countries. Indonesia was in 7th rank.¹ World Health Organization (WHO) estimated 1.9-2.2 millions children death from acute respiratory infection (ARI) every year.^{2,3} Pneumonia as cause of death in 1.3 million children under five years old and 81% death occurred in two years of first life.⁴ According to Demography Health Survey 2012, infant mortality rate in Indonesia was 32/1000 live births and under five years old mortality rate was 40/1000 live births. Proportion of pneumonia death was 9.4%. Basic Health Survey (2013) got periods prevalence of pneumonia under five years old 18.5/1000 population and the children who got treatment only 1.6/1000.^{5,6}

New emerging respiratory virus is potential become global health security threat such as Severe acute respiratory syndrome/ SARS, Avian influenza H5N1, H7N9, H1N1pdm09, Human Adenovirus-14 and Middle East Respiratory Syndrome/MERS CoV.⁷⁻⁹ One of SARI caused is influenza virus as important pathogen in public health. Influenza is also zoonotic infection such as Avian Influenza that circulates endemic in poultry, sometimes evoke an outbreak in human and can result pandemic. The most common prevalence of Influenza in school age children but the severe disease can happen in infant, elderly people, and high risk person with comorbid.^{10,11} Seasonal influenza was second common caused in children with pneumonia and substantial contribute to hospital admission and cause of death in children under five years old.^{4,12} Experience from influenza pandemic H1N1 2009 lead many countries including Indonesia, to raise pandemic awareness through Influenza Like Illness/ ILI and SARI surveillance. SARI was clinical syndrome of acute respiratory

infection that caused by influenza virus or other pathogens.¹⁰

In high risk people such as children, elderly people, and chronic disease, influenza can be severe and fatal. There were about 3-5 million severe cases and 250-500 thousand of death every year.¹³ Influenza outbreak can reached more than 49,000 of death and 200,000 people need hospital admission every year, only in USA.¹¹ WHO estimated 20% of hospitalized children under five years old with SARI and 90% of SARI was pneumonia. Some studies in several country along with WHO, showed that Influenza has biggest proportion in children under five years old with SARI.¹³⁻¹⁵

Countries with four seasons like Europe and America have more clearly influenza data and the peak of Influenza was in winter. But the information was limited in tropical and subtropical developing countries. In WHO South East Asian Region (SEAR), influenza with severe pneumonia episode 273 thousand (78-1094 thousand) and proportion of severe cases was 5%, while death was about 49 thousand and proportion was 11.1%.⁴ In Indonesia, Influenza were identified 20.1% of ILI cases and 21.7% of SARI cases in 2003-2007.¹⁶ In 2011, influenza positive were confirmed 6% of SARI cases.¹⁷ In 2013-2015, influenza positive were confirmed 11.8% of SARI cases from six hospital sentinel site and 15% were pneumonia. 40% of influenza positive were in age group 1-4 years.^{18,19} This proportion was high enough but still influenza related pneumonia was unrecognized and underreporting as well. Objective of the study is to elaborate the risk factors of the influenza related pneumonia in children under five years old.

METHOD

The pneumonia control program in Ministry of Health focuses on early detection and treatment for bacterial pneumonia in community. Severe acute respiratory infection (SARI) can develop fatal pneumonia. We collected data from the pneumonia surveillance database in the Acute Respiratory Infection sub directorate.

RESULTS

Etiology

Pneumonia can be caused by bacteria, virus, fungi and can be caused by other things such as radiation, aspiration.^{2,20} The most common bacteria were *Streptococcus pneumoniae* (30-50%) and *Haemophilus influenzae* (10-30%) and both of them can be prevented by vaccine. In some severe cases caused by *Staphylococcus aureus* and *Klebsiella pneumoniae*.^{9,21,22} The most common virus were Respiratory Syncytial virus/ RSV in 15-40% hospitalized pneumonia in developing countries, followed by Influenza A and B, parainfluenza, Human metapneumovirus and adenovirus.^{9,21}

Risk Factors

Definite risk factors were age less than two years, asplenia or hyposplenia, diabetes, Influenza, HIV, humoral immune defect, malnutrition, low birth weight, inadequate breast feeding, no measles vaccine, indoor air pollution and crowding. The likely risk factors were chronic diseases (asthma, neurologic disorder, tuberculosis), zinc deficiency, concomitant diseases, poverty, mother experience, mother age. The possible risk factors were mother low education, child day care, vitamin A deficiency, humidity, latitude, cold weather and outdoor air pollution.^{13,20-22,23-26}

Symptoms

Mostly, people with mild Influenza has mild symptom and recovery in two weeks. Some will develop to severe outcome and need hospitalization. The highest severity was in infant and who have comorbid diseases. Acute symptoms and fever often persist for 7 to 10 days. Weakness and fatigue may linger for weeks. Influenza usually occurs in winter outbreaks or epidemics (in temperate climates). Fulminant fatal influenza viral pneumonia occasionally occurs; dyspnea, cyanosis, hemoptysis, pulmonary edema, and death may proceed in as little as 48 hours after the onset of symptoms.²⁴

DISCUSSIONS

Seasonal influenza circulates worldwide but only influenza A and B can cause outbreak in human and have vaccine to prevent it. Influenza A is more important pathogen that cause seasonal, endemic infections and periodic, unpredictable pandemics.^{13,27,28} According to seasonality, common pattern of RSV and Influenza were highest in rainy season, although Influenza circulates around the year.^{9,19}

Pneumonia caused by combined of risk factors that associate with host, infection and environment.²¹ Influenza risk factors were children under five years old particularly children less than two years old, person with comorbid such as chronic lung diseases, heart diseases, liver disease, kidney disease, diabetes, asthma, neurological disorders, blood disorders, HIV/AIDS, immune deficiency, obesity.^{13,26}

Co-pathogenesis between influenza and superinfection bacteria was based on multifactor. Virulence factor that showed virus has specific strain effect on host that which allows bacterial infection caused pneumonia. Influenza virus cause multiple changes in lung that can caused secondary bacterial invasion. Epithelial cells damaged, surfactant disruption, cell pieces into airway become access and source of nutrition to bacteria growth. Airway physiology changes reduce oxygen exchange, airway hyper reactive and reduce bacteria cleaning mechanism. Influenza virus can facilitate bacteria from upper respiratory inhale and invasion to lower respiratory.²⁹ Influenza A viral replication peaks approximately 48 hours after inoculation into the nasopharynx and declines slowly, with little virus shed after about six days. The virus replicates in both the upper and lower respiratory tract. Even after the infectious virus can no longer be recovered, viral antigen can be detected in cells and secretions of infected individuals for several days. Non-fatal influenza viral infection predominantly involves the upper respiratory tract and trachea, but fatal cases of influenza usually show evidence of pneumonia.²⁴

In pneumonia, alveoli filled with pus and fluid that cause disturbed oxygen exchange and dyspnea. Lung compliance reduce and will manifest as fast breathing. If condition getting worst, lung will more rigid and chest retraction appear. Viral infection signed by mononuclear cell accumulation in sub mucous and perivascular room that produce airway partial obstruction. Alveolar type II cell damage and surfactant production reduce so that appears hyaline membrane and lung edema.^{6,29,30}

Influenza can be manifest as asymptomatic to serious illness with systemic symptoms. Seasonal influenza has sudden onset of fever (38-40°C), cough, muscle ache, joint pain, sore throat and cold. Pneumonia can develop in few hours, usually caused by secondary infection. Pneumonia symptoms were dyspnea, cyanosis, lung edema, acute respiratory distress syndrome and death can process in 48 hours after the onset. Hospitalization and death depend on some factors that accompany such as age and comorbid (asthma, pulmonary disease, cardiovascular disease, neurological disorder, metabolic disorder).^{11,13,22,24,30-32}

In Indonesia, pneumonia diagnosis base on clinical condition such as fast breathing and chest retraction. Age divided according to Integrated Management of Childhood Illness (IMCI) age group to determine fast breathing. The classification pneumonia by fast breathing which were age <2 months: ≥ 60 times/ minute; age 2-<12 months: ≥ 50 times/ minute; age 12-<60 months: ≥ 40 times/minute.^{6,33} Chest X-ray, blood test and culture, rapid diagnostic test for pneumococcal with immunochromatography assay, reverse transcriptase polymerase chain reaction/ RT-PCR, DNA assay as supporting examination can be used if available. Chest X-ray was unable to differentiate bacteria or virus.^{10,20,22,26,34-36} Ultrasonography (USG) can diagnose accurately pneumonia cases in children and adolescence and can replace Chest X-ray for diagnoses.³⁰ The diagnostic method such as Polymerase Chain Reaction (PCR) enhance new virus detection and

vaccine for pneumococcal and Haemophilus influenzae reduce bacterial pneumonia and increase virus pneumonia.⁹

Mostly, Influenza is mild and recovery in two weeks with supportive treatment such as nutrition and liquid and home care. Grossly, the children that treat as outpatient get oral antibiotic. In randomized study, 820 mild pneumonia in children with Amoxicillin 50 mg/weight two times a day as effective as three times a day. Nutrition for severe pneumonia or respiratory distress give through nasogastric tube or intravenous line. Tight monitoring is needed to avoid overhydration.²⁶ Intravenous antibiotic such as Ampicillin or cephalosporin give to inpatient patient depend on local resistance.^{26,30} Treatment for Community Acquired Pneumonia were optimum supportive and effective antibiotic as soon as possible. Supportive treatments were oxygen, ventilator, volume resuscitation, vasopressor, nutrition can save life.^{20,22} According to Ministry of Health, severe pneumonia in health care center (Puskesmas) must refer to hospital as soon as possible after give prompt treatment such as oxygen, antibiotic first dose, antipyretic and other supportive drugs if available.⁶ Length of stay in pneumonia with abnormality of chest X-ray longer than normal chest X-ray.³⁵

Antiviral for influenza can be used as treatment and prophylaxis to reduce serious complication and death.²⁴ Ideally, antiviral given in first 48 hours since the onset. There were two class of drugs. First, Matrix 2 ion channel blocker (Adamantanes) which were Amantadine and Rimantadine, but about one third patient has drug resistant. Second, Inhibitor Neuraminidase consist of Oseltamivir and Zanamivir, while Peramivir and Laninamivir only have license in several countries. Oseltamivir dose in age 0-8 months was 6 mg/kg body weight per day, divided in 2 doses; age 9-23 months: 7 mg/kg body weight per day, divided in 2 doses; ≥ 24 months : 4 mg/kg body weight per day, divided in 2 doses; premature baby: 2 mg/kg body weight per day, divided in 2 doses for 5 days.³⁴

Pneumococcal vaccine was recommended for age 7-12 months and given twice with 2 months interval. For age >1 year, it is given one time. Both age groups need booster one times after age >1 year or two months after the last time vaccine. For age >2 year only gives one times.^{24,37} Children were primary reservoir for pneumococcal colonization in human, and eliminate carrier status will reduce transmission to population.²²

Influenza vaccine was recommended for children more than 6 months. Vaccine was give protection for several months normally, because virus mutation gradually make population immune disappear after several years. Booster vaccine are recommend for high risk people.²⁴ The most effective influenza vaccine if similar with circulate virus. WHO is always update vaccine compositions every two years. Since 2013-2014, quadrivalent vaccine compositions has been recommended to give more protection.¹³

Influenza virus changes constantly and need surveillance to monitor virus influenza in human. Influenza surveillance is important to early detection and evaluate new virus variance or subtype.¹³ ILI and SARI Surveillance were used WHO guidelines for case definition. Because of limited resources, many countries use sentinel surveillance to monitor Influenza. ILI surveillance is for monitor outpatient and SARI surveillance is to monitor inpatient.¹⁰ According to International Health regulation/IHR, every country should report influenza data to WHO through FluNet for laboratory result data and Fluid for epidemiology data.^{10,38-40}

Indonesia has SARI surveillance called as Surveilans ISPA Berat Indonesia (SIBI). SIBI has developed according WHO guidelines since 2013 in six sentinel hospitals around Indonesia. The sentinel hospital were RSUD Deli Serdang, RSUD Wonosari, RSU Kanudjoso Djatiwibowo, RSUD Bitung, RSUP NTB, RSU Dr. Haullussy Ambon. As a model, SIBI in the future can be expanded for other emerging

respiratory infection in order to pandemic preparedness and awareness.^{41,42}

CONCLUSION

Pneumonia remains high morbidity and mortality in children under five years old. Influenza is important caused of pneumonia and need to monitor through surveillance. Influenza has high proportion in children under five years old in Indonesia. The effect of influenza related pneumonia is still unclear.

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