International Islamic Medical Journal
Journal Homepage ://journal2.unusa.ac.id/index.php/IIMJ

Parasitic Disease and COVID-19 Syndemics in Indonesia: Biomedical Aspects

Reqgi First Trasia[1*]

[1]Division of Parasitology, Faculty of Medicine, Universitas Sultan Ageng Tirtayasa
*Corresponding Author: reqgi.first@untirta.ac.id
DOI: 10.33086/iimj.v5i1.5068

ARTICLE INFO

Keywords: Syndemics, Parasitic disease, Covid-19, biomedical, Tropical disease

Submitted: Sept 3rd 2023
Reviewed: Sept 12th 2023
Accepted: Oct 26th 2023

ABSTRACT

Background: Syndemics happened while two or more coinfections have dangerous interaction and lead to a harmful outcome than for either single infection. In Indonesia, during COVID-19 pandemic, it has deal with a doble burden presume to neglected tropical disese (NTD) control. Parasitic disease as a part of NTD must be a concern in Indonesia along pandemc. There are still few articles that review the biomedical aspects of co-infection COVID-19 with parasitic diseases in Indonesia, whereas an understanding of biomedical aspects can encourage knowledge about pathogenesis which will make an earlier diagnosis.
Results: This review summarize how parasites may serve as protective agents or risk factors in pandemic and, vice versa, how the COVID-19 may disturb the prevention and misdiagnosis of parasitic disease in Indonesia. Co-infection COVID-19 with malaria increass the burden of severe clinical manifestations and poor prognosis due to exaggerated proinflammatory response. Coinfection triggers TNF and IL-6 to activate coagulation cascade leading to micro-thrombosis and coagulopathy. Besides, helminthiasis causes vary configuration of immune-modulation, thereby lowering susceptibility to other infections and tolerating COVID-19 better. They modify Th2 respons to limit pro-inflammatory cytokines, such as IL-6 which is observed in severe cases of COVID-19. T-cell hypoactivation in SARS-CoV-2 and *W.bancrofti* will cause relatively mild manifestation of COVID-19.
Conclusions: In parasite infection, the IL-4 may elevate and induce shadow memory CD8+ T-cell (TVM cell) for CD8 response rapidly agains virus. It control human IL-4 or IL-10 that leads to the maturation of Th2 cells and down-regulation of the inflamation respons of IFN-γ, IL-17 and TNF-α. These mechanisms allow us to blockade the cytokines storms observed in COVID-19 cases.

Introduction

Synergistic endemics happened while two or more coinfections have dangerous interaction and lead to a harmful output than for other single infection. For instance, Epstein Barr Virus (EBV) and malaria co-infection may leads to Burkitt's lymphoma because EBV loads can be increased by malaria which stimulate B-cell proliferation. Besides that, HIV-infected person confluence a lot frequency of increased HIV viral load subsequent severe manifestation of *Plasmodium falciparum* infection. Some of HIV-parasite

coinfections were correlated with worsened immunosuppression and increased HIV viral load. (Hussein, et al. 2020)

Many kinds infectious agents can independently and simultaneously invade host body. Because parasites and microorganisms share mechanisms of pathogenesis, raising up allergic or immune reactions and inflammatory processes, it is reasonable that coinfections can lead to under-diagnosis and misestimates of the true prevalences of single infectious agent. That coinfections can led to a harm course of manifestation. The emergence of new infective agent gives a defiance for both the health care system and researchers effort to estimate its long-term health and epidemiological problems. That agent were followed by happening risk factors, lead to a more harmful symptoms and need new a diagnostic approach. One of currently come snarl was the SARS-CoV-2 disease in this recent pandemic. (Gluchowska, et al. 2021)

COVID-19 which caused by SARS-CoV-2 which has rapidly deployment to elevate than 200 countries worldwide, resulting in 596.873.121 people being infected and 6.459.684 deaths (as of August 30th, 2022). Amongst Southeast Asian countries, Indonesia was one of the aloft elevating rates of COVID-19 incidences. Based on data gotten from the Indonesia Ministry of Health on September 1st, 2022, Indonesia has 6.354.245 COVID-19 confirmed cases and 157.541 deaths. (Kemenkes, 2022)

Prior to the COVID pandemic, it was a distinct category of contagious disease that got a few considerations, in spite of affecting more than 140 nations and infecting a lot of people, called by Neglected tropical diseases (NTDs). There are 15 parasitic and vector-borne disease which included in the category of NTDs based on the 10th Meeting the Strategic and Technical Advisory Group for NTD: Dengue, Chagas, chikungunya, trypanosomiasis, soil transmitted helminthiases (STHs), onchocerciasis, lymphatic filariasis, schistosomiasis, echinococosis, taeniasis/ neuro-cysticercosis, food-borne trematodiases, chromoblastomycosis, mycetoma, visceral and cutaneous leishmaniasis. (WHO, 2022)

Most prevalent NTDs were founded in low-income nations, including Asia, Africa, and Latin America. NTDs were as usual found in tropical area because of their climate and humidity, which is appropriate habitats for the expansion of the disease. People whose have little accessibility to pure water and whose get along at district no right management regarding human waste were potential to be infected. As long as the pandemic, work to eradicate NTDs has been upset. In 2021, WHO suggest some recommendation concerning this emergency condition, substantially propose

the use of continuous health promotion, community-based engagement, and participative case find out. Eradication of NTDs has to implicate such potent cooperation between citizens and health stakeholder. Hence, WHO push authorities of local health to reinforce NTDs platforms, health campaigns and surveillance management. (UNICEF, 2020)

COVID-19 interfere the program, for example ITNs and SMC distribution. Malaria diagnostic and management were also interfered because of the hazard faced by health workers who serve during pandemic. Resolution makers will be necessary to produce complicated choices to make sure COVID-19 and continuous malaria endemics were did when lowering the risk to communities and health workers. The community-based action towards malaria diagnosis, prevention, and treatment has important character to present in respons to COVID and were critical to match individuals on-going health care, especially for sick people. Applicating approaches of delivery would need to be gotten for some action changes in the contexture of pandemic. (Hussein, et al. 2020)

Indonesia encounter a double burden as a tropical country. For example, the management of NTDs concatenated with the present of COVID-19 will remain a public health problem. In October 2022, some province in Indonesia suffered the rainy season, that escalate the any vector borne disease survival rate, like helminths and mosquitoes that bring causative agent. Furthermore, based on the Indonesia Ministry of Health, three parasitic NTDs were exist in Indonesia, including lymphatic filariasis, schistosomiasis, and STHs. (Riskesdas, 2019) This review will present the readiness of Indonesia in facing NTDs along the pandemic based on biomedical aspect.

Results

Biomedical Aspect of COVID-19 and Helminthiasis

Because SARS-CoV-2 infectious disease manifested by fever accompanied by cough and difficult to breath, it may be misdiagnosed for other respiratory disease. In other side, identical symptoms are monitored in some parasitoses. Parasitic infection not only cause malnutrition and anemia, destroy tissue, influence immune system, but also support viral infectious and disturb vaccines effectiveness. Nevertheless, immune-modulation of parasite will be take care of us from organ damage by minimizing inflammation responses. (Mohamed et al, 2020)

Filariasis

Filarial worms are a species of nematode that causes an infectious disease

called filariasis. Vectors transmitting these parasite include *Culex sp, Anopheles sp, Aedes sp* and *Mansonia* sp. The species that cause the most cases in Indonesia are *Brugia malayi.* Currently, WHO data show that 892 million people from 48 countries in 2019 were suffered filariasis, and they need therapy to quit the transmission. This parasite may infect person by infective stage of larva from mosquito bites. Moreover, children more often to be infected and experience silent decay in their lymphatic system. (WHO, 2022)

In tropical regions with many species of vectors like Indonesia, filariasis was still a health issue. In 2020, it were 591 recent filariasis cases, where 10.679 prolonged cases from the prior year. The Papua province possess the first number of chronic cases, followed by East Nusa Tenggara, East Java, West Papua and Aceh. The amount of filariasis cases in 2020 is 10.845 cases. (Figure 1) Beside that, the incidence in Indonesia filariasis is <1% for 10.000 resident in 2019. (Kemenkes, 2020)

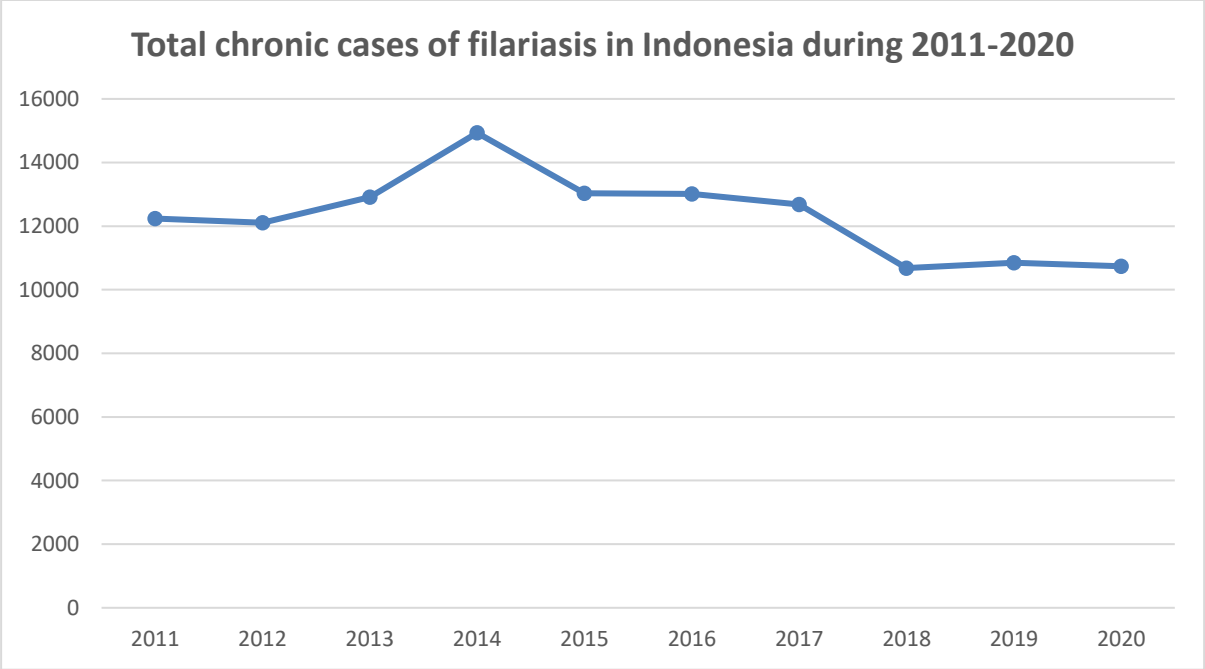

Figure 1. Total Filariasis Chronic Cases during 2011-2020 in Indonesia

An obligatory effort to eradicate lymphatic filariasis was been tried via large-scale therapy within at-risk community annually. A combination of diethylcarbamazine, albendazole and ivermectin regimen have been suggested by WHO to overcome filariasis in endemic countries. This method may destroy the microfilariae in the blood of infected individual so that the transmission may be stopped. Indonesia have worked to eradicate filariasis since fifty years ago, but it still faces challenge. For example, lack of personnel of health worker, cooperation

related the geographical boundaries in Indonesia, low of health promotion, lack of awareness and inadequate medication. (Kemenkes, 2020)

The WHO recommended to delay community-based program on April 1, 2021, as well as case surveillance action and mass drug therapy promotion in tropical countries with NTD up to farther notice. Accordingly, the preparation of interim MDA which used on filariasis eradication programs were postponed to. Nevertheless, WHO purpose to anatomize effect of delaying delivery of MDA at 2030 by thinking others way to empowering program, later intend to decline the bad effects of the pandemic. Relatively, by postponing this program, the WHO is speed up progress by annual MDA or through elevating access to the drug until 65% of the population at risk. (WHO, 2022)

Elephathiasis is examined etiology of chronic morbidity, infirmity and permanent disability, lead to societal stigma. The early stadium is signed by lymphangitis, chest pain, coughing, and fever. Leucocytosis and massive blood eosinophilia are also present. Likewise, infection of *Wuchereria bancrofti* that cause tropical pulmonary eosinophilia was also signed by eosinophilia, body weight loss, chest pain, fever, and coughing. CT-scan of the thorax shows bronchiectasis, calcification, mediastinal lymphadeno-pathy, and trapped air. (Mullerpattan et al, 2016)

Soil Transmitted Helminths (STHs)

STH disease still slender in some rustic areas in Indonesia. A study at Sampang District on 2020 showed an elevated incidence (71,3%) of STH disease among toddlers. (Kurniati et al, 2020) Another research in Central Sumba Regions showed that the STH incidence was 91% of disease occurred in children. (Mau F, 2019) In addition, there are still 23 countries where preventive chemotherapy (PC) coverage is under the target of WHO as of 2019. One of them is Indonesia. Beside that, compare to that in 2018, the world PC coverage is decline from 60% to 57%. (WHO, 2021)

COVID-19 pandemics impended the detention of NTD, a condition that was a great health issue for subtropical and tropical regions, where parasite infection, like NTDs and STH are frequent and co-incidences are commonly occur. This situation will lead to a bad outcome, which is called to as syndemic (synergistic endemics). (Gutman, et al. 2020) Commonly, STH infection arrange host IL-10 and IL-4 cytokines, which resulting in downregulation of proinflammatory response of TNF-α, IL-17, IL-6 and IFN-γ. This regulation permit us to inhibit the helminth both systemically and locally. Nevertheless, IL-6 storm monitored in

COVID-19 cases was prompt to prevent the inhibition. This condition will go on in person whose infested by parasites and remain in rural area with mass drug administration was not held regularly. (Trasia RF, 2020)

In resolving to the pandemic, Indonesian Ministry of Health has suggested guidance. The objective of this regulations are suggestion for cooperation of crss-sectoral in spreading efforts to stop SARS-CoV-2 transmission, applicating emergency situations and daily services for children along the pandemic. Daily health services for children were done by implementing the triage strategies, physical distancing, transmission control and prevention. In districts where the government applies imposing Pemberlakuan Pembatasan Kegiatan Masyarakat (PPKM), the administration of preventive chemotherapy is held by applying health protocol for control of COVID-19 and physical distancing. Those programs are held by school-based community and integrated health service (as known as Pos Pelayanan Terpadu in Indonesian). (Kemenkes, 2021)

Ascariasis is largely disseminated infestation of the ileum caused by *Ascaris lumbricoides.* Some infective stage of its larva are released in the host ileum. From this, they penetrate the abdominal wall and adjourned via vascular to alveoli, where it molt and grow. Throughout transmission, the human may suffered muscle pain, paleness, chills, dyspnea, breathlessness, fever and coughing. A prevalent symptoms are Loffler's syndrome, a self-limiting pulmonary eosinophilia correlated with lung inflammation. (Lamberton, et al. 2017) The adjourning larvae may stimulate lung-granuloma and tissue-granuloma conformation with eosinophils, neutrophils, and macrophages, lead to peribronchial inflammation and hypersensitivity, with bronchospasm and elevated bronchial mucus production. (Cheepsattayakorn et al, 2016)

Hypereosinophilia was a primary manifestation of ascariasis enabling to differentiate with leucopenia associated COVID-19. The thorax roentgen will show pulmonary infiltrates. In severe ascariasis, a group of helminths may blockade a segment of human ileum. These may suffer colic or abdominal cramping and vomitus. (Lamberton, et al. 2017)

The migration of hookworm in human bloodstream resulting in symptoms which are be confusd with COVID. On this incidence, th infective larva permeate thrugh skin, entering vein, and carried away to lungs and heart. The unique signs made by moving larva are identical to pulmonary ascariasis, involving Loffler's syndrome, expectoration and coughing, aside from

symptoms of bronchitis: wheezing, malaise, fatigue, headaches, general weakness, joint pain, muscle aches, and fever. Then if cough up and swallowed, larva feed on blood in small intestine, lead to iron-deficiency anemia or protein deficiency, which can result in facilitation co-infection, like SARS-CoV. Existence of adult helminth in ileum can rsult in loss of appetite, blood in feses, nausea, abdominal cramps, colic and severe pain. (Tan X, et al. 2019)

Diagnosis of strongyloidiasis must be done with attention. *Strongyloides stercoralis* invasiveness complies an identical way to *Ancylostoma* larvae infestation. Nevertheless, feature hang on the severity of infestation and manifestation diverge among cases. (Cimino et al, 2020) None the less, symptoms of pneumonitis or bronchitis, fever, coughing, and eosinophilia were particularly found when larva move to alveolus. Infestation of Strongyloides may be not apparent clinically. The common gastrointestinal feature such as stomachache, constipation, vomiting and nausea. Immunodeficiency individual is more tend to present with syndrome of hyperinfection because of disseminated strongyloidiasis and where parasitic burden elevated by autoinfection. The spread form is signed by the helminth may be found in atypical predilection, like the central nervous system, heart, muscle, and liver. (Karanam, et al. 2020)

Doctors should be mindful that tocilizumab and corticosteroid therapy may make easier strongyloides infestation, lead to disseminated infection and hyperinfection. There ara two cases of Strongyloidiasis declared in COVID-19 patients: one in an old man who showed disseminated infection after methylprednisolone and tocilizumab therapy (Lier, et al. 2020), and another a woman from Italia after tocilizumab and dexamethasone treatment. (Marchese, et al. 2020) In endemic area, person infected by COVID-19 must be detected for Strongyloides infestation before therapy. A probable alternative for patients at risk was a colaboration of the administrating antiparasite prophylaxis and serological testing as prevention strategy. (Stauffer, et al. 2020)

A study suggest that effect of STH infestation on both Th2 and Th1 immunity is important be aware in designing vacines agains SARS-CoV, especially in STH-endemic nations. These inference is promoted by showed something for the developing of Th2 immuno-pathology pathway and triggering Th1 response in controlling replication of virus. Chronic STH infections are founded to enhancing a type 2 respons of immunity such as IL-9, IL-6, and IL-5, resulting in suppressiveness

of the immune respons agains virus. Besides that, STH and COVID coinfection might lead to heavy outcome, especially in a population with malaria. (Fonte, et al. 2020)

STH infection requires many kinds of immunomodulation, lead to an elevated susceptibility to other infections, alteration in the severity of allergic, inflammatory and autoimmune disease. It was argued that STH infestation may resulting in good tolerance of SARS-CoV infection and inadequate responses to vaccines. (Maizels, 2020) The interleukin storm showed in heavy incidence of COVID is figured by pro-inflammatory cytokine, like IL-6. Nevertheless, it was probable which STH infestation might modifying the outcome of infection by modulating Th2 respons to prevent the inflamatory substance. It will be especially happened at countries which STH infestations are still exist. (Siles-Lucas, 2021)

Schistosomiasis

Schistosoma japonicum is the cause of schistosomiasis in Indonesia, which is also widely distributed in some other Asian countries. Schistosomiasis was endemic in two districts in Indonesia, Poso (Bada and Napu valley) and Sigi (Lindu valley), which are in the Province of Central Sulawesi. Statistic from 2012-2019 (Figure 2) declare a generality in the incidence of schistosomiasis in Central Sulawesi. The latest statistic show that the incidence of schistosomiasis has decline. (Nurwidayati, 2019)

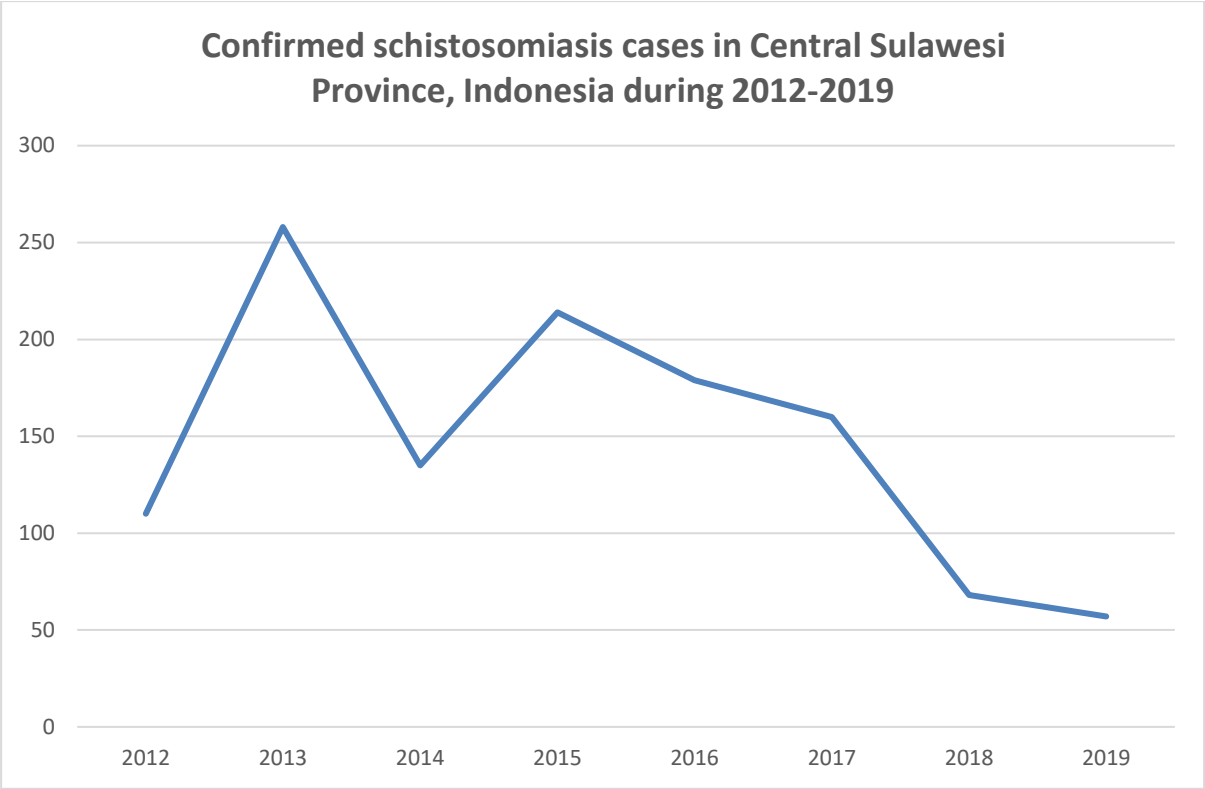

Figure 2. Confirmed Schistosomiasis Cases in Central Sulawesi, Indonesia during 2012-2019

Waters do an important part in spread and transmission of schistosomasis. Host-to-surroundings transmision specially happen when infested person defecate on fresh water and contaminate it with their stool which contain worms egg. Then the larvae stage of the helminth may penetrate via host skin during contact with those waters. Cercariae is the free-swimming and short-lived larval stages of trematodes, it is shed by slug which play role as mediate host for worms. This larva need 5-6 week to differentiate to adult schistosoma. Then the big helminth may be in person vein for until three years. The mate Schistosoma may generate thousands eggs every day. A little amount of eggs may stimulate immune reactions and destruction in human organ, while another egg was released from the body through stool. (CDC, 2022)

The manifestation of schistosomasis is outcome of imune response to helminth's egg. Many people having no complain while he/she is first infested, but may suffered an itchy skin and rash during several days after becoming ill. Moreover, some systemic complain can develop within 1-2 months of transmission, such as cough, muscle aches, chills, and fever. Without appropriate therapy, these features may be prolong and exist during any months in host organs. (Colley, et al. 2016)

Clinical feature of schistosomiasis include diarrhoea, haematochezia, and

stomach ache. In heavy cases, enlargement of the spleen and liver can be happened. Magnification of the hepatic is usually correlated to hypertension of the stomach vein and liquid accumulation in the peritoneal cavity. Another side, schistosomasis may exist as uro-genital manifestation too, by connected urinary infection feature like ureter and bladder fibrosis, and haematuria in severe cases. Uro-genital schistosomasis happen in female and uniquely appear as nodules in the vulva, pain during sexual intercourse, vaginal bleeding, and genital injuries. (Nelwan, 2019)

Diagnostic methods for this commonly use worms detection from the urine and faeces with urine microscopy, antibody detection in the serum, antigen and DNA detection, or Kato-Katz technique. This Kato-Katz is the most widely used test because of its diagnostic sensitivity, easy to used, and cheap. Furthermore, immunological and serological based testing might be use in stating exposur to the transmission in nonendemic districts. (Ajibola, 2019)

Person respiratory system may be infected by flukes of schistosomiasis which establish similar feature to COVID-19. Most incidence of schistosomiasis is no complain or just appear as only rash. A study observed eight patients have pulmonary manifestation with reporting dyspnea, dry cough, nausea, lymphadenopathy, loose faeces with blood, enlarged hepatic and vomiting, without fever or with nocturnal fever sometimes. The chronic infection was figured by blood in the urine or faeces, enlarged liver, anaemia, and abdominal cramp. Nodule is also appear in the lungs range at 2-15 mm in size and has grond opacity halo. The feature of intestinal schistosomiasis are non-specific, include malnutrition and dyspepsia. (Niemann, et al. 2012)

A study show a low amount of COVID incidence in districts when schistosomiasis is syndemic. This might suggested a probable protection effect toward COVID. [36] Similar to other flukes infection, Schistosoma obtain a hunch Th1 respons in earlier stadium of infection. [37] That has been observed which worms may enhanc mechanism of antiviral, resulting in a better viral load control. During helminthiasis, IL-4 may elevate and situation TVM cell so fast CD8 response agains antige enconter. Most possible, helminthiasis has stimulate the host imune reaction to thrive a safe mechansm base on inductive of high responsiveness virtual memory CD8+. These will counter the anti-inflammation impact associated to immunity type two, so that lead to more efficient anti-viral response. Low mortality of COVID in Africa can be correlated to immunomodulation of inflamatory proceses

by helminths releasd molecule. (Fonte, et al. 2020)

The treatment method of schistosomiasis in Indonesia consist of praziquantel dose regimen (60 mg/kg BW). On 2012, a research in Central Sulawesi show praziquantel was suggested therapy toward all phase of schistosomasis. Nevertheless, researches on another drugs were still need because time of evaluation was so long. (Nurwidayati, 2019) Kemenkes has announced a promotion to eliminate schistosomasis. Synergy and collaboration sectoral are significant, like community, government and public health. Before pandemic, treatment of schistosomasis was difficult. The COVID can exacerbate NTDs that switched both human and financial resources. Great planning must be indicated to take care the collaborative among the prevention of both NTDs and pandemic. (Bapennas, 2019)

Biomedical Aspect of COVID-19 and Malaria

All species of Plasmodium obtain identical symptoms over infection, such as general malaise, body aches, vomiting, nausea, headaches, sweats, chills and fever, with the onset varies to the genus. Most serious feature is respiratory malaria which has similar manifestation with COVID at endemic districts. On some incidence, bilatral pulmonry infiltrate may be shown on thorax roentgen. A study explained any cases of malaria with pulmonary infiltrates and bilatral fluffy pulmonry infiltrate. Infectious may result in the destruction of erythrocyte and anemia, which aggravate COVID-19 comorbidity and lead to poor prognosis. On the contrary, it has also been forecasted that pandemic can lead to more than 36% malaria mortality over five years opposed with the situation before pandemic. (Sanklecha, et al. 2013)

A significant factor in patient diagnosed malaria was ARDS. Besides that, the similarity of COVID-19 and malaria manifestation may lead to one disease being misdiagnosed, or the probability that comorbidity may be missed. Meanwhile, patient with malaria has anti-GPI antibody which may find SARS-CoV glycoproteins. This can make a good character agains COVID or improve disese cours. As shown, in districts while malaria is endemic, chloroquine and hydroxychloroquine propylaxis can has curative or preventive effects against SARS-CoV-2. (Hussein, 2020)

Notified from many studies has observed which are interferon secreted by lymphocyte as immune reaction to transmission by any strain of malaria. This interferon has in vivo and in vitro eficacy agains the corona responible for COVID-19, SARS, and MERS. Glycosyl-

phosphatidyl-inositol (GPI) molecules targeted by IgG antibodies from malaria patients acts particularly via stimulating leucocytes, causing the proinflammatory cytokines release and triggering the expression of Toll-receptor (TLR) 4 and 2. SARS-CoV has vary glycoprotein (GPs). These might be knew by anti-GPI antibody leading to milder disease feature or protecting against viral infection. (Gomes, et al. 2016)

Because of the identically feature between COVID-19 and malaria, particularly headache, fatigue, shortness of breath and fever of acut onset, a COVID-19 patients might be mis-diagnosed as malaria on the contrary. Furthermore, complications such as multiorgan failure, septic shock, and ARDS could also ocur at both COVID and malaria. Primary step to find a COVID patients is the symtomatic surveillance, which are myalgia, headache, sore throat, dry cough, fever, dyspnea in at-risk population such as healthcare workers and person with a history of close contact with confirmed cases. Nowadays, individual suffered fever might be test for COVID-19 and then back house because of a nonreactive results, rejecting the probability of malaria. In other hand, febrile person might get test for malaria when she/he actualy has SARS-CoV-2 infection. A third probable condition is that an individual might has malaria and COVID-19 coinfection, but the treatment and diagnosis can result in missing the other. (Gostic, et al. 2020)

In malaria, when schizonts rupture and release merozoits in blodstream, this lead to chills and another features of malaria. Therefore, manifestation of malaria is because of the relase proinflamatory cytokine, such as IL-12, IL-6, IFN-γ, and TNF. Several studies in endemic regions has conclude that it was important to has a balanc betwen host anti-inflammatory Th2 response (IL-10 and IL-4) and pro-inflamatory Th1 respons (IL-12, IL-6, IFN-γ, and TNF). The massive Th1 response is often cause severe symptoms of malaria. Similar appears to COVID-19 cases, suggesting that comorbidity also result in massive immunological response which lead to heavy features and bad prognosis. (Jin, et al. 2020)

ARDS visible in nearly 25% of adults and 40% of children with malaria falciparum. It has some causes, such as metabolic acidosis, anaemia, coinfection with pathogen-related pneumonia and sequestraton of infested eritrosit (RBC) in the pulmonary capillary. The manifestation ranges from mild to severe upper respiratory symptoms. ARDS both in malaria and COVID-19 is because of inflammatory elevated permeability of capillary and endothelial damage. Due to this condition, Plasmodium – SARS-CoV-2

coinfections might result in fast decadence and bad outcome. Consequently, coinfection can lead to heavy COVID-19 and physicians must keep this in mind. (Jin, et al. 2020)

Some virus infection, such as SARS-CoV, release a pro-coagulan through induced any factor expresion, bring about endotelial disfunction or activating of TLR. Increased D-dimer, prolongation of prothrombin time, and fibrin degradation products levels are correlated with a bad outcome. Relatively, malaria was also correlated with procoagulant state. The IL-6 and TNF activate coagulate cascad, which is similarly to the disese course. Disease of malaria is regularly correlated with complication of micro-thrombotic. Nevertheless, large vessels thrombosis such as pulmonary embolism and cerebral venous thrombosis have been observed. (Lippi, et al. 2020)

The release of molecule from breakdown endotelial cell or damage of activate platelet in malaria producing a coagulan condition, same as mechanisms in COVID. Thus, Plasmodium-SARS-CoV co-infection can lead to more severe degree of coagulopathy. Hence, it requires increasing sensitisation on potent of malaria-COVID comorbidity. In view of that malaria testing is more avalable, which is better if healt worker do test of malaria while them suffered on COVID. This condition is especially relevan for person in endemi country and travellers. It provides a opportunity to response to several infection disease forehanded and decline avodable mortality and complications. (Hussein et al, 2020)

Effect of COVID-19 on Parasitic Disease Diagnostic and Prevention Program

The WHO released a general suggestion on April 2021 to disrupt all actions for control of NTDs program, in spite of high prevalence of humans disease. (Figure 3)

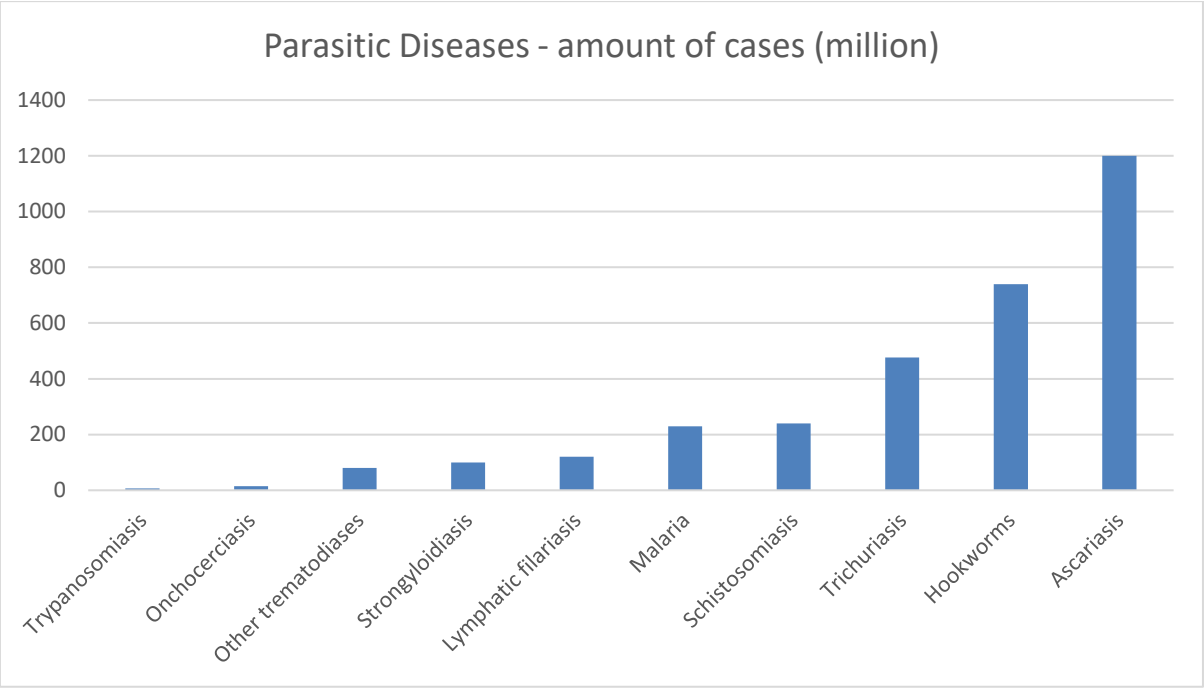

Figure 3. Estimation of Existing Parasitic Disease Worldwide (source: WHO/CDC)

These have reversely impact roadmap of any NTD, include that concering parasite infestation, have result in disappear of some achievemen. Furthermore, parasite infection has been widely excluded from the tasks of health services at the regional and national levels. Nevertheless, as malaria prevention program is threatened by COVID-19 pandemic, there was a constan purpose to evade malaria outbreak. A study conclude that pandemi might resulting in extra 205 milion malaria incidence and 378.900 deads at Africa. (Sherrad, et al. 2020)

STH diseases (STDs) and schistosomasis are two other NTDs which control and prevention programs have impact by local and global respons effort to lower dissemination of COVID. Even though an interference in the prophylaxis therapy of STD would just temporarly effect improvement toward WHO 2030 target, program must be started as early as posible to lessen impact on mortality. When this interference, aditional time would be need to deal with the increasing infestation level. (Malizia, et al. 2021)

Parasitological diagnostics has influenced by the COVID-19 pandemic. Because a lot of laboratory are need perform SARS-CoV test, it have to postpone or minimize its particular parasitology testing duty, that have important effect on amount of confirmed case of human parasitic. The lessened in the amount of order and diagnostic test of parasitologic was noticable in some laboratory. (Gluchowska, et al. 2021)

Plasmodium infection is a considerably endemic disese in east of Indonesia. Outbreak of COVID may led to disruption in health-care system on malaria, indecorous treat and non-treated malaria incidence, consequence in elevate in morbidity and mortality. Malaria prevention measure which might lower the load on health-system also in background of COVID such as presumptif malaria therapy and MDA. (Hussein, et al. 2020)

There are modalities to convey these intercession. The sesonal malaria chemopreventive and insectcide-treated nets were presented through population-large promotion while other intercession were accompanied thrugh patient centre mode. Execution of these malaria program was influenced by the lockdown and travel restrictions during the pandemic. The implementation of these programs have to examine the weightiness of both maintaining the safety of health care workers and decreasing malaria-related deaths. Action shuld be managed in the way which keep away meeting of resident without dwelling by precaution. Action which elevate risk of COVID or were not easy to applicated with no break protectif measure shuld be interrupted. (WHO, 2020)

To confirm repercussion of malaria service, national malaria program shuld pick up COVID-19-related recomendations which enhnce malaria control service by confirming safety to service teams, patients, and clients, while doing case management action and malaria prevention to the most extent probable. For example, ensuring the best testing and management of malaria patients. Malaria therapy and prevention was more significant along COVID pandemic than under normal conditions. So that, all procedur must done when keeping safety to patients and healt worker in the situation of SARS-CoV-2 transmission. (WHO, 2021)

The latter-day strategy of Indonesia goverment to decrease contagion of COVID consis of implementation of healt protocol, such as wash hand, stay at home, minimize outdoor activities, wear masks, physical distancing, suspend travel activity, and stay updated in relation to COVID-19. Furthermore, large-scale physical distancing has been implemented widely in districts with high prevalence, based on Government Regulation. The total amount of tests done until September 3rd, 2022 is 6.280.183 tests. The fiasco to decline the transmission of SARS-CoV-2 lead to highest activ case, which is 176.367 case on September 3rd, 2022. The current update on September 3rd, 2022 show number of BOR is at their worst also, with most severe rating report in Jakarta is 79%. The real case of COVID-19 in Indonesia seems like to be underestimated because of lack testing. The large gap between the amount of suspected

cases and person tested indicates that capacity of testing in Indonesia still limited. (WHO, 2022)

As aforesaid, there are four parasitic NTDs in Indonesia which need the beginning of a specific eradication program. Because of pandemi, Indonesian require to perform smart efort to efficient manage of NTDs. Nevertheless, there is no guideline for strategic to overcome NTD in Indonesian along pandemic. There is also no number of NTDs cases reported during pandemic. Next healt police stakeholders must use these in care, because the accessibility of data as baseline was significant in creating a new strategy. A research in Jakarta show an elevation in deaths due to COVID with up to 59% compared with the previous year. Even though, the fatality rate is less than developed countries because of Indonesia demographics, which is dominated by adult age group. On the whole, there was no hesitation that surveillance for new cases NTDs detection would be interfered during the pandemic, like surveys for STH and filariasis. (Elyazar, et al. 2022)

To reduce death cases due to late response, Indonesia must strengthen its means at control of NTD. Team work was key for success control of NTD during the pandemic. The citizens and government must cooperate on case tracing, and may use the integrated data centres. If online networking was limited in endemic districts, another effort may be the use of short message services. (Martindale, et al. 2019)

Conclusion

The in spite of being a fatal disease, COVID-19 remains be misdiagnosed as other infection because of its novelty, especially affecting respiratory system, such as schistosomiasis, malaria, strongyloidiasis, and filariasis. Along COVID pandemi, Indonesian yet deal with any defiance for the control of NTDs, particularly parasitic disease, such limit observation on follow-up of MDA in filariasis, miscoordination in eradication STDs or delayed evaluative of medication use for schistosomasis. (Fauziah et al, 2021) This article prompt to the Indonesia goverment to reinforce its work in NTD controls via other design, like collaboration on stakeholder in detecting recent cases. Tracing, testing or treatment to decline the COVID-19 transmission should be remedy, so that gap of COVID-19 suspect and confirm case may be declined. If it happen, then NTD control and case detection of parasitic infection may be done efficiently.

References

Ajibola O, Gulumbe BH, Eze AA, Obishakin E. Tools for detection of

schistosomiasis in resource limited settings. Med Sci (Basel) 6: 39 (2018)

Centres for Disease Control and Prevention. Parasite Schistosomiasis. https://www.cdc.gov/parasites/schistosomiasis/disease Accessed September 7th, 2022

Cheepsattayakorn A, Cheepsattayakorn R. Parasitic pneumonia and lung involvement. Biomed Res Int. (2015) 874021

Cimino RO, Fleitas P, Fernandez M, Echazu A, Juarez M, Floridia-Yapur N, Cajal P, et al. Seroprevalence of the Strongyloides stercoralis infection in human from Yungas Rainforest and Gran Chaco Region from Argentina and Bolivia. Pathogens (2020) 9, 394

Colley DG, Bustinduy AL, Secor WE, King CH. Human schistosomiasis. Lancet 383: 2253-64 (2015)

Fauziah S, Putri SMD, Salma Z, Wardhani HR, Hakim FKN, Sucipto TH, Aquaresta F, et al. How should Indonesia consider its neglected tropical diseases in the COVID-19 era? Hopes and challenges (Review). Biomed Rep 14:53 (2021)

Fonte L, Acosta A, Sarmiento ME, Ginori M, Garcia G, Norazmi MN. COVID-19 Lethality in Sub-Saharan Africa and Helminth Immune modulation. Front Immunol (2020) 11, 574910

Gluchowska K, Dzieciatkowski T, Sedzikowska A, Deniziak AZ, Mlociki D. The new status of parasitic disease in the COVID-19 pandemic – Risk factors or protective agents? J Clin Med (2021) 10:2533

Gomes LR, Martins YC, Ferreira-Da-Cruz MF, Daniel-Ribeiro CT. Autoimmunity, phospholipid-reacting antibodies and malaria immunity. Lupus. (2015) 23:1295-8

Gostic KM, Gomez ACR, Mummah RO, Kucharski AJ, Lloyd-Smith JO. Estimated effectiveness of symptom and risk screening to prevent the spread of COVID-19. Elife (2020) 9:e55570

Gutman JR, Lucchi NW, Cantey PT, Steinhardt LC, Samuels AM, Kamb ML, Kapella BK, et al. Malaria and parasitic neglected tropical disease: potential syndemics with COVID-19? Am J Trop Hyg 103: 572-7 (2020)

Hussein MIH, Albashir AAD, Elawad OAMA, Homeida A. Malaria and COVID-19: unmasking their ties. Malar J (2020) 19:457

Indonesia Ministry of Development Planning and Agency: Bappenas. Siaran Pers Roadmap Eradikasi Schistosomiasis (2018) Wujud komitmen Pemerintah atasi penyakit demam keong, Jakarta, Indonesia.

Indonesian Ministry of Health: COVID-19, https://covid19.go.id/ Accessed September 1st, 2022

Indonesian Ministry of Health: Data dan Informasi Profil Kesehatan Indonesia 2020. Jakarta, pp1-213 (2021)

Indonesian Ministry of Health: Profil Kesehatan Indonesia tahun 2019, pp107-8 (2019)

Indonesian Ministry of Health: Situasi Filariasis di Indonesia. Infodatin Pusat Data dan Informasi Kementerian Kesehatan RI. Pp1-12 (2020)

Indonesian Ministry of Health. Panduan pelayanan kesehatan balita pada masa tanggap darurat COVID-19. Kementerian kesehatan Indonesia, pp 1-30, 2020.

Jin Y, Yang H, Ji W, Wu W, Chen S, Zhang W, et al. Virology, epidemiology, pathogenesis, and control of COVID-19. Viruses (2020) 12;372

Karanam LSK, Basavraj GK, Papireddy CKR. Strongyloides stercoralis hyper infection syndrome. Indian J Surg (2020) 12,1-5

Kurniati M, Budiono B, Sulistyawati SW: Intestinal protozoa infection in relation to nutritional status of the students Mandangin Island elementary school 6 in Sampang Regency. JUXTA J Ilm Mhs Kedokt Univ Airlangga 10: 25 (2020)

Lamberton PHL, Jourdan PM. Human ascariasis: Diagnostic update. Curr Trop Med Rep. (2016) 2, 189-200

Lier AJ, Tuan JJ, Davis MW, Paulson N, McManus D, Campbell S, Peaper DR, et al. Case report: Disseminated Strongyloidiasis in a patient with COVID-19. Am J Trop Med Hyg (2020) 103, 1590-2

Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe COVID-19 infections: a meta-analysis. Clin Chim Acta (2020) 506;145-8

lyazar IR, Surendra H, Ekawati L, Djaafara BA, Nurhasim A, Hidayana I, Widyastuti W, et al. Excess mortality during the first ten months of COVID-19 Epidemic at Jakarta, Indonesia. medRxiv 69:1-13, (2022)

Maizels RM. Regulation of immunity and allergy by helminth parasites. Allergy (2020) 75, 524-34

Malizia V, Giardina F, Vegvari C, Bajaj S, McRae-McKee K, Anderson RM, de Vlas, et al. Modelling the impact of COVID-19 related control programme interruptions on progress towards the WHO 2030 target for soil transmitted helminths. Trans R Soc Trop Med Hyg. (2021), 115, 253-60.

Marchese V, Crosato V, Gulletta M, Castelnuovo F, Cristini G, Matteelli A, Castelli F. Strongyloides infection

manifested during immunosuppresive therapy for SARA-CoV-2 penumonia. Infection (2020) 1-4

Martindale S, Mableson HE, Kebede B, Kiros FH, Tamiru A, Mengistu B, Krueger A, et al. A comparison between paper-based and m-Health tools for collecting and reporting clinical cases of lymphatic filariasis and podoconiosis in Ethiopia. mHealth 4: 49 (2018)

Mau F. Prevalence and intensity of soil-transmitted helminth infections among elementary school students in West Sumba and Central Sumba districts East Nusa Tenggara, Indonesia. J Med Sci Clin Res 5 (2018)

Mohamed MFH, Mohamed SF, Yousaf Z, Kohla S, Howady F, Imam Y. COVID-19 unfolding filariasis: The first case of SARS-CoV-2 and Wuchereria bancrofti coinfection. Plos Negl Trop Dis. (2020) 14, e0008853.

Mullerpattan JB, Udwadia ZF, Udwadia FE. Tropical pulmonary eosinophilia – A review. Indian J Med Res. (2015), 138, 295-302

Nelwan ML. Schistosomiasis: Life cycle, diagnosis, and control. Curr Ther Res Clin Exp 91: 5-9 (2019)

Niemann T, Marti H, Duhnsen S, Bongartz G. Pulmonary schistosomiasis – Imaging features. J Radiol Case Rep (2011) 4, 37-43

Nurwidayati A, Frederika PP, Sudomo M. Fluktuasi schistosomiasis di daerah endemis provinsi Sulawesi Tengah tahun 2011-2018. Buletein penelitian kesehatan 47: 199-206 (2019)

Sanklecha M, Mehta N, Bagban H. Varied presentation of complicated falciparum malaria in a family. Indian Pediatrics (2013) 49, 413-4

Scheer S, Krempl C, Kallfass C, Frey S, Jakob T, Mouahid G, Mone H, et al. Schistosoma mansoni Bolsters Anti-viral immunity in the murine respiratory tract. PLoS ONE. (2015)

Sherrad-Smith E, Hogan AB, Hamlet A, Watson OJ, Whittaker C, Winskill P, Ali F, Mohammad AB, et al. The potential public health consequences of COVID-19 on malaria in Africa. Nat Med (2020) 26,1411-6.

Siles-Lucas M, Gonzalez-Miguel J, Geller R, Sanjuan R, Perez-Arevalo J, Martinez-Moreno A. Potential influence of Helminth moleculeson COVID-19 pathology. Trends Parasitol. (2021) 37, 11-4

Ssebambulidde K, Segawa I, Abuga KM, Nakate V, Kayiira A, Ellis J, Tugume L, et al. Parasites and their protection against COVID-19, Ecology or Immunology? MedRxiv (2020)

Stauffer WM, Alpern JD, Walker PF. COVID-19 and Dexamethasone: a potential strategy to avoid steroid-related

strongyloides hyperinfection. JAMA (2020) 324, 623

Tan X, Cheng M, Zhang J, Chen G, Liu D, Liu Y, Liu H. Hookworm infection caused acute intestinal bleeding diagnosed by capsule: a case report and literature review. Korean J Parasitol. (2018) 55, 417-20.

Trasia RF. Covid-19 dan Koinfeksi Penyakit Parasit. Med Hospitalia J Clin Med 7: 298-303 (2020)

WHO: 2030 Targets for soil-transmitted helminthiasis control programmes. 2021.

WHO: Lymphatic Filariasis. https://www.who.int/health-topics/lymphatic-filariasis Accessed September 4th, 2022.

WHO: WHO issues interim guidance for implementation of NTD programmes. https://www.who.int/neglected_disease/news/LF-reporting-continued-progress-towards-elimination Accessed September 6th, 2022.

WHO. Coronavirus Disease 2019 situation report, 48. WHO 19:1-20, (2022)

WHO. Responding to community spread of COVID-19. Interim Guide 8 March 2020;1-6

WHO. Tailoring malaria interventions in the COVID-19 response. https://www.who.int/publications/m/item/tailoring-malaria-interventions-in-the-covid

World Health Organization and the United Nations Children's Fund (UNICEF): Community-Based Health Care, including Outreach and Campaigns, in the context of the COVID-19 Pandemic. Geneva, p39, 2020.

World Health Organization. Neglected tropical disease. Accessed August 2022 https://www.who.int/neglected_disease.