A Systematic Review of the Epidemiology of Human Respiratory Viruses in Indonesia

Sankalpa Bhattarai[1], Hsien-Yao Chee[1], Andrew Prasettya[2], Elvan Wiyarta[2], and Benjamin Anderson[1]

[1]Duke Kunshan University
[2]University of Indonesia

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Abstract

Viral pathogens greatly contribute to higher respiratory disease burden among individuals living in low-to-middle income countries (LMICs). In Indonesia, influenza-like illness (ILI) and severe acute respiratory infection (SARI) surveillance networks have been established to better understand the epidemiology of viral respiratory disease; however, due to limited resources and operational capacity, data from these systems are sparse. Here, we summarize the results of a literature review conducted to identify published articles related to human respiratory viruses in Indonesia. We identified 66 scientific articles, published between 1998 and 2021. Of these, 21 (31.8%) studied influenza A or B, 17 (25.8%) studied influenza H5N1, 19 (28.8%) studied coronaviruses, 5 (7.6 %) studied RSV, and 2 (3.0 %) studied enterovirus. Our findings show that large numbers of studies in Indonesia were primarily conducted in response to viral respiratory disease outbreaks, but with limited epidemiological data. We also identified gaps in information regarding the geographical distribution of viral respiratory disease burden, as studies were more highly concentrated in populated cities, such as Jakarta, Java, and Bali. This review highlights the need for more robust surveillance of ILI and SARI cases throughout Indonesia, as well as allocation of more resources for viral respiratory disease etiology and epidemiological studies.

Introduction

Respiratory viruses are a leading cause of morbidity and mortality among children and adults worldwide [1, 2]. The burden of respiratory viruses is disproportionately high in low-to-middle income countries (LMICs) [3, 4]. Specific respiratory virus infections (RVIs), such as influenza and respiratory syncytial virus (RSV), and more recently SARS-CoV-2, are the major contributors to this high burden of disease [3, 4, 5]. In 2018, influenza virus accounted for 870,000 influenza-virus-associated hospital admissions, 15,300 in-hospital deaths, and around 34,800 overall influenza-virus-associated acute lower respiratory infections (ALRI) deaths among children under 5 years of age [6]. Around 82% of in-hospital deaths due to influenza virus occurred in low-income countries (LICs) and LMICs [6]. Whereas, it is estimated that RSV accounts for 33 million cases and 118,000 deaths annually in children under five, of which 22 million cases and 103,000 deaths are in LICs and LMICs [7]. In addition to the annual impact of common respiratory viruses like influenza and RSV, emerging respiratory viruses such as avian influenza A (H5N1) virus, influenza A(H1N1) pdm09 virus, MERS-CoV, avian influenza A(H7N9), and most recently, SARS-CoV-2 represent elevated threats to global health security [1, 8]. Collectively these viruses markedly contribute to respiratory disease morbidity and mortality in populous countries like Indonesia[9, 10, 11].

Indonesia is a tropical archipelago of islands with high humidity and a population of around 271 million [12]. Indonesia has year-round respiratory virus activity with seasonal peaks ranging between October and April, which corresponds with the wet and dry seasons [13]. More recent surveillance efforts have shown dominant

seasonal influenza activity occurring December through February with clear patterns of phased infections among the different seasonal influenza virus strains (influenza A/pH1, influenza A/H3, and influenza B) [10, 14]. Far less is known about the epidemiology and burden of RSV and other respiratory viral infections in Indonesia as comprehensive surveillance for non-influenza viruses is limited. Indonesia also has a growing population of animal reservoirs for zoonotic infections including poultry, rodents, wild birds, dogs, pigs, and monkeys [15]. Given that Indonesia is an LMIC with a large and diverse population, the risk of viral respiratory disease burden is high. Therefore, this literature review was conducted to better understand the epidemiology of viral respiratory disease in Indonesia.

Methods

Search Strategy and Selection Criteria

Following PRISMA guidelines, a systematic online search of English and Indonesian language databases were conducted. For the English journals, a search of three scientific abstract indexing databases (PubMed, Web of Science, and CAB Abstracts), with no restriction on the year of publication, was performed on 23 February 2021 using the following structured search query ((virus or viruses or viral) AND (respiratory) AND (Indonesia)).

For the Indonesian language journals, a search of the Garuda database, with no restriction on the year of publication, was performed on 03 February 2021. Garuda is a comprehensive database operated by the Indonesian Ministry of Research, Technology and Higher Education, which contains various national publications from all universities in Indonesia. Given that the database lacked the functionality to use a multi-string structured search query, the single term "virus" was instead used. Thereafter, a manual review and selection strategy was performed based on the inclusion and exclusion criteria.

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria for English and Indonesian language journal articles included published scientific journal entries which were also epidemiological investigations or clinical case reports conducted on humans in Indonesia. All reviews, commentaries, perspectives, and personal opinions were excluded, along with any entry that was a diagnostic assay evaluation.

Article Screening and Reconciliation

For the English language journals, articles from the three databases were first screened by two reviewers (SB and HY) to remove all duplicates. Articles were then independently evaluated and sorted by the same two reviewers based on the inclusion and exclusion criteria. Both reviewers then reconciled search results together to determine the final list of entries. For the Indonesia language journals, two reviewers (AP and EW) worked independently to screen the entries according to the inclusion and exclusion criteria. Both reviewers then reconciled search results together to determine the final list of entries.

Results

Search Results and Study Selection

For English language journals, a search conducted on February 23, 2021, yielded a total of 732 results, of which 196 publications were from PubMed, 109 from Web of Science, and 427 from CAB Abstracts. After removing 417 duplicates, 315 articles remained of which 226 failed to meet the inclusion criteria leaving 89 articles. A full text review of the remaining 89 articles resulted in 23 articles being removed resulting in a total of 66 remaining articles (Figure 1).

For the Indonesian language journals, a search conducted on February 3, 2021 yielded 6,068 publications from Garuda. After removing 5,930 irrelevant articles and 28 duplicates, 110 publications remained. Those articles were irrelevant because they are not related to respiratory viruses. These were screened, and a total of 50 articles that did not meet initial inclusion were excluded, resulting in 60 articles. After full text screening, of 60 articles, 58 articles were excluded resulting in only 2 human-focused articles. These two

articles were also included in the English language search results. Therefore, the final number of articles from both databases remains at 66 (Figure 2).

Study Location

In this review we found 29 (43.9 %) of the 66 studies were conducted exclusively in Jakarta. Similarly, 47 (71.2%) studies were performed on Java Island (West, Central and East) and 12 (18.2 %) studies were conducted in Bali. Yogyakarta was included in 14 (21.2 %) of the 66 studies and 9 (13.6 %) other studies were performed on West Nusa Tenggara. East Nusa Tenggara Timor was represented in 1 (1.5 %) of 66 studies, while only 3 (4.5 %) studies were conducted on the Island of Papua. In addition, 7 (10.6 %) of the 66 studies were part of larger global, regional or multinational studies and 17 (25.8 %) studies were conducted at multiple locations across Indonesia. An additional 5 (7.6%) studies were performed using secondary data from Indonesian-wide databases which included the Ministry of Health Avian Influenza H5N1 case database and archival samples from the National Institute of Health Research and Development (NIHRD) (Figure 3).

Study Characteristics

Articles included in this review were published between 1998 and 2021. Only 1 of the 66 (1.5 %) articles were published between 1998 and 2000, while 15 of the 66 (22.7%) articles were published between 2001-2010 with the remaining 50 (75.8%) articles being published between 2011- 2021 (Figure 3).

Of the 66 articles, 38 (57.6%) articles studied influenza viruses, of which 21 (55.3 %) were focused on influenza A or B, and 17 (44.7%) were conducted on avian influenza H5N1. In addition, 19 (28.8%) of the 66 total articles were conducted on coronaviruses. Of the 19 coronavirus papers, 17 (89.5%) articles studied the SARS-CoV-2 virus while 2 (10.5 %) studies were conducted on Middle East Respiratory Syndrome (MERS). Furthermore, 5 (7.6 %) of the 66 articles studied RSV and 2 (3.0 %) of the 66 articles studied enterovirus. Of the 2 enterovirus studies, 1 (50.0 %) was on human rhinovirus, and 1 (50.0 %) studied on coxsackievirus virus. Finally, 1 (1.5 %) out of the 66 total articles examined torque teno virus and 1 (1.5 %) study was conducted on cytomegalovirus.

Study Population

Among the 66 articles included in this review, 64 (96.9%) articles specified their study populations. Out of these 64 articles, 52 (81.2%) articles included children and adults aged from <1 year to 71 year as study participants. The majority of articles included both males and females as study participants. Out of 64 articles, 10 (6.4%) articles examined patients with SARI and 10 (6.4%) articles examined patients with ILI. Among 64 articles, 3 (4.6%) articles studied workers in live animals markets or swine and poultry farms. There were 7 (10.6%) articles that focused solely on rural populations as study participants, while 6 (9.0%) articles included both rural and urban populations as study participants.

Sample Size

Twenty-four (36.4%) of the 66 studies had a sample size greater than or equal to 500, 22 (33.3%) studies had a sample size less than 500, and 7 (10.6 %) studies were part of larger global, regional, or a multinational studies. In addition, 12 (18.2%) of the 66 articles in our review were case reports which included SARS-CoV-2 infected individuals or patients as study participants.

Discussion

In this literature review, articles were searched and summarized to better understand the epidemiology of respiratory virus infections in Indonesia. After reviewing the final 66 articles, we found that most of the studies focused predominately on influenza A and B, RSV, avian influenza H5N1, and SARS-CoV-2. Fewer studies were conducted on enterovirus, torque teno virus, and cytomegalovirus.

The first study reporting on the epidemiology of influenza A or B in Indonesia was conducted in Papua in 1998 [16]. Subsequent studies that have been published have prioritized Jakarta[17, 18, 19, 20, 21, 22, 23] and Bali[13, 18, 24, 25] as the main study locations. Only after the 2009 influenza H1N1 pandemic did studies on

seasonal influenza increase. These studies were primarily conducted via hospital-based surveillance, with children and elderly as the main study population[10]. Data from these studies show that peak prevalence tended to coincide with the rainy seasons [17, 22], and males were more likely to experience ILI than females[26]. Meanwhile, in rural areas, there was also increasing patterns of influenza infections in households with young children and poultry [27]. Although, seasonal influenza has been identified as an important contributor to acute respiratory disease in Indonesia [13, 21], and 20% of total cases of respiratory disease are attributed to influenza A and B in all regions of the world [28]. A 2011 study showed that influenza virus only contributed to 6% of 333 SARI cases in Indonesia[20]. A lack of reliable surveillance data was acknowledged as a primary reason for this discrepancy with regional and global averages [20, 28]

The studies on influenza H5N1 were primarily conducted in Jakarta and Bali [21, 22, 29, 30, 31] at the time of a national outbreak that occurred in 2006. Influenza H5N1 studies published after the outbreak included some new epidemiological studies, but also retrospective studies that used primary data from the outbreak[21, 22, 32, 33]. Data from the outbreak reports show that sporadic family clusters had a higher proportion of case fatality[29, 34] with mild-moderate variations in symptoms[13, 29, 30, 35], which especially occurred in patients under 18 years of age [22, 30] and among poultry workers[36] who had direct or indirect contact with infected poultry[30, 37]. Although, there was no strong evidence of human-to-human transmission [31], antiviral regimens were given as early as two days following the onset of non-specific symptoms [38, 39]. The mortality rate of influenza H5N1 infections among humans was still very high [32], increasing from 73% in 2005 to 100% in 2012 [33].

Our review found a large number of SARS-CoV-2 papers that were published in response to the global pandemic that began in January of 2020. We also found that the majority of SARS-CoV-2 studies were conducted in densely populated areas of economic and national significance such as Jakarta [40, 41, 42, 43, 44, 45] Yogyakarta[46, 47], and the islands of Java (West Central and East) and Bali [48, 49, 50, 51]. Our review did not include any SARS-CoV-2 studies examining lesser populated provinces like North Kalimantan, Maluku, and West Papua which could indicate a gap in funding and infrastructure required to conduct epidemiological investigations away from populous urban centers. In terms of study populations, the majority of studies were case reports of SARS-CoV-2 patients. Studies like Baskara et al. 2021 [46] found that treating SARS-CoV-2 patients in low-resource settings was challenging due to a lack of ventilation support and intensive care facilities. In these settings, there are additional difficulties in distinguishing the clinical characteristics of SARS-CoV-2 from other respiratory diseases like tuberculosis. Other case reports highlight the radiological findings and benefits of using chest X-ray's in screening for SARS-CoV-2 among patients [47] while others describe the potential for misleading diagnoses when using unconventional methods like chest CT scans to detect SARS-CoV-2 [42].

Most SARS-CoV-2 studies were conducted on younger and middle-aged adults below the age of 65. These included Widysanto et al.[52], Putra et al. [43] and Kadriyan et al. [53]. As for older population groups (>65 years old), Tenda et al. [45] included an individual that was 71 years old, while Rozaliyani et al.[44] examined individuals from all age groups and found that older age, dyspnea, pneumonia and pre-existing hypertension were associated with death from SARS-CoV-2. The study also described how the number of deaths decreased in the weeks after the implementation of large-scale social restrictions thus supporting the efficacy of such interventions. Gunadi et al. [54] found that 39 of 60 (65%) SARS-CoV-2 samples from Indonesia had the D614G mutation which was recently discovered to be more transmissible than previous variants, which is the only report included in our review that evaluated SARS-CoV-2 variants [55]. Anggraini et al.[48] and Somasetia et al. [50] focused specifically on high-risk population groups where they observed that a low neutrophil-to-lymphocyte ratio decreases the risk of SARS-CoV-2 in pregnant women, and reported a case of a 6-year old child being co-infected with SARS-CoV-2 and dengue. Our review did not find any studies that evaluated the transmissibility or case fatality rate of SARS-CoV-2. It may be that this type of epidemiological data is not publicly accessible.

Studies included in our review indicated there is a significant burden of a lower respiratory tract illness (LRI) caused by RSV among the children in Indonesia [56, 57, 58]. Provinces with high population densities

such as West Nusa Tenggara, and West Java were represented in most of the RSV studies [56, 57, 58, 59, 60]. Our review indicated that the incidence of RSV related to LRI in Lombok island and Bandung city is lower in children less than 6 months of age compared to the older children [56, 57, 59]. In addition, Simoes et al. [57] reported a higher RSV incidence among children in rural areas compared to urban areas. Studies from Djelantik et al. [59], Wertheim et al.[61], and Widhidewi et al. [24] reported that the peak of RSV cases occurred during the rainy season (March to July). However, there were no consistent conclusions regarding the association between seasonality and the occurrence of RSV disease in Indonesia. A study from Omer et al. [58] reported an association of rain with a 64% higher incidence of RSV disease (incidence rate ratio 1.64, 95% confidence interval 1.13-2.38), whereas, Simoes et al. [57], and Djelantik et al.[59] reported no association of RSV outbreaks with humidity, temperature, or rainfall. Therefore, further investigations are required to determine the seasonality of RSV in Indonesia.

Few studies included in this review evaluated the epidemiology of enterovirus [62, 63], torque teno virus[64], and cytomegalovirus virus [42]. Most of these studies were conducted among children less than 5 years of age who were hospitalized with ILI or SARI in Jakarta and Java[42, 62, 64], but information regarding seasonality and transmission dynamics for these viral groups is not available. Enteroviruses, including EV68, EV71, coxsackieviruses, rhinoviruses, echoviruses, and polioviruses, are the important viral group that may have the potential for zoonotic transmission between animals and humans[65, 66].

Indonesia, like most countries in the world, has developed ILI and SARI surveillance networks under the WHO's Global Influenza Surveillance and Response Systems (GISRS) [13]. This network was designed to improve influenza disease control by providing support on epidemiology, research, influenza vaccine recommendations, laboratory diagnostic tools, antiviral, and public health risk assessment. However, due to challenges such as cost-effectiveness, complex computer networking and technical expertise requirements, and limited diagnostic capacities of clinical laboratories, the ability of this network to provide robust data on emerging and endemic respiratory viruses in Indonesia has been limited. Furthermore, most of the surveillance activity in Indonesia is conducted using hospital based surveillance as a response to frequent outbreaks of influenza subtypes and sporadic cases of RSV from July to November [61]. As a result, there is more concentrated information on influenza viruses and RSV viruses, but sporadic or missing data for other common respiratory viruses. Additionally, limited information is available regarding the environmental persistence of influenza, RSV, and other respiratory viruses outside hospital settings. As a result, there remain large gaps of information regarding the epidemiology of respiratory viruses in Indonesia.

Our review identified only two papers from the Garuda database that evaluated the epidemiology of human respiratory viruses in Indonesia. This suggests that language is not the primary reason that data on this topic is not largely available in research journals. Additionally, our review indicated a concentration of studies conducted mostly in populated and economically developed areas, such as Jakarta, Bali, Java, (West, Central, and East), Yogyakarta, and West Nusa Tenggara. Limited research has been reported on populations living in less developed areas. In evaluating the studies, a clear publication trend was observed, where there would be a surge in published papers after a viral outbreak has occurred in Indonesia. This trend can be observed with the outbreaks of SARS in 2002-2004, avian influenza in 2005-2006, influenza A H1N1 in 2009, and most recently with SARS-CoV-2. A large proportion of the studies in our review are based on outbreak based passive surveillance, retrospective studies, hospital level ILI, and SARI surveillance systems. Fewer studies use active surveillance approaches.

Overall, our review showed a surprisingly low number of published papers assessing the epidemiology of viral respiratory pathogens in Indonesia. Of the studies included, the majority were conducted in urban centers of high population density and economic significance. Our findings also indicated a clear publication trend where papers have been published only after a large viral respiratory disease outbreak has occurred. Fewer papers have been published assessing the seasonal burden of viral respiratory disease. These observations indicate a great need to further enhance surveillance capacity for viral respiratory diseases in Indonesia to better track and characterize this important disease burden.

Data availability statement

No datasets were generated or analyzed during the current study.

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Conflict of Interest Disclosure

The authors report no conflicts of interest.

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Table 1. Summary of articles included in the review.

Author and Reference	**Study Location**	**Sample Size**	**Specimen Sources/ Sample Type**	**Targeted pathogens**	**Virus Identified**	**Study Population**	**Type of study**	**Findin**

Corwin et al. 1998 [16]	Irian Jaya	NA	NA	influenza virus	influenza A	Young adults between 15–44 years of age	Outbreak reporting, Case and control study	Young adults a 15–44 y account for the largest percent of influe virus outbrea related deaths
Djelantik et al. 2003 [60]	Lombok Island	2677	Nasopharyngeal washes	RSV	RSV	Children between 0-2 years of age with severe lower respira-tory illness	Hospital based passive surveil-lance study	For children 0-1 and 0-2 years of age, the esti-mated inci-dence o severe RSV LRI hospi-taliza-tion wa 25 per 1000 child-years and 14 per 100 child-years respecti
Djelantik et al. 2003 [59]	Lombok Island	4351	NA	NA	RSV	Children 0-2 years of age admitted for pneumonia	Population based ret-rospective cohort study	Among children hospital ized for pneumo age < 4 months hypoxia were identifie as highe risk fac for deat

Beckett et al. 2004 [17]	Jakarta, West Java, Yogyakarta, Makassar, Sulawesi, and Bali	1544	Nasal and pharyngeal swabs	influenza virus	influenza A (H1N1 and H3N2)	Adults (age, >14 years) and children (age, 4–14 years) with respiratory symptoms	Laboratory based passive surveillance study	Peak prevalen of influ infectio tended coincid with th respecti rainy seasons
Robertson et al. 2004 [56]	West Java	640	Nasopharyngeal specimens	RSV	RSV	children between 0- 5 years of age	Hospital based passive RSV surveillance	The incidence of RSV- associat LRI per 1000 child-years was 34 in Indonesia In Indonesia and Mozambique, RSV cases occurre primarily during the rainy season
Kandun et al. 2006 [29]	Jakarta	8	Serum, nasaland , throat swabs, tracheal aspirates	influenza A H5N1	influenza A H5N1	Patients between 1-38 years of age with avian influenza H5N1 infection	Outbreak investigation	Cluster human infectio with cl 2 H5N1 viruses include mild, severe, fatal ca amongs family membe

Sedyaningsih et al. 2007 [34]	West Java, North Sumatera	598	Throatand, nasal swab, serum, endotracheal aspirates and washes, lung-biopsy	influenza A H5N1	influenza A H5N1	Patients with suspected H5N1 virus infection with a median age of 18.5 years.	Outbreak investigation	Sporadi and fam clusters cases of avian influenz H5N1 infectio with a l case-fatality proport occurre through Indones during 2005–20
Giriputro et al. 2008 [30]	Jakarta	296	NA	influenza A H5N1	influenza A H5N1	Children and adults 1- 40 years of age	Retrospective case series	Most patients were younger and had indirect contact with infected poultry. The majorit of cases were pre-sented to the hospital after having systemi inflam-matory respons syn-drome (SIRS)

Kandun et al. 2008 [38]	Indonesia (location not defined)	127	NA	influenza A H5N1	influenza A H5N1	Patients with a median age of 20 years with H5N1 infection	Case series	Early ic tificatio suspect cases fo treatme was difficult because the very low inciden the influenz and the commor occurre of ILI
Omer et al 2008 [58]	Lombok island	2878	Nasopharyngeal swabs	RSV	RSV	Hospitalized children between 0-2 years of age	Hospital based passive surveil-lance study for Haemophilus in-fluenza type B (Hib) project	Statisti associa-tion of monsoo associat weather with localize RSV out-breaks sug-gested local factors influ-ence RSV disease transmi
Santhia et al 2009 [31]	Bali	87	Serum, cloacal, tracheal swabs, throat and nasal swabs	influenza A H5N1	influenza A H5N1	Household partici-pants from village with H5N1 outbreaks; Humans, Birds (poultry), pigs/swine survey at live bird markets	Behavioral, virological and seroepi-demiologi-cal survey	Transm of H5N humans remaine rare eve despite high lev of hand both healthy sick bir

Adisasmito et al. 2010 [39]	Throughout Indonesia	93	NA	influenza A H5N1	influenza A H5N1	Laboratory-confirmed H5N1 influenza cases with median age of 18 years	Observational study	Fatality due to influenza A H5N1, may be related to delay in initiation of treatment after presenta
Dilantika et al. 2010 [18]	Jakarta, Java, Yogyakarta, Bali, Sulawesi, North Sumatra	733	Stool samples, nasal and throat swabs	influenza virus	influenza A (H1N1 and H3N2) Influenza B	Pediatric patients (0-6 years of age) presenting with concurrent diarrhea and influenza-like illness	Hospital based passive surveillance study	In child the influenz virus infectio may be localize the gastroin testinal tract ar cause pediatri diarrhea
Ramadhany et al. 2010 [19]	8 provinces of Indonesia	549	Nasal and throat swabs	influenza virus	i influenza A (H1N1) and influenza B	SARI patients	Hospital based passive SARI surveillance	There w 21 (4%) cases caused influenz and 12 (2%) caused influenz

Vivi et al. 2010 [36]	Jakarta, Sukabumi	711	Sera	influenza A H5N1	influenza A H5N1	Poultry farmers and workers in poultry processing facilities	Observational study	Poultry workers were fou to have asymp-tomatic H5N1 v infectio but no antibod were detecte among poultry farmers
Yupiana et al. 2010 [37]	Java	794	NA	influenza A H5N1	influenza A H5N1	Humans and poultry	Descriptive epidemi-ological study and out-break investigation	Human infectio with avian in-fluenza H5N1 was as-sociate with poultry outbrea
Aditama et al. 2011 [67]	Throughout Indonesia	139	NA	influenza A H5N1	influenza A H5N1	Risk factors for avian in-fluenza H5N1 infection were an-alyzed among a popula-tion all age groups.	Outbreak investigation	Avian in-fluenza H5N1 infectio is influ-enced by, and may even depend on, host genetic suscepti

Simoes et al. 2011 [57]	Kota Bandung	2014	NA	RSV	RSV	Children between 0-5 years of age	Cohort study	In children between 0-6 months old, the incidence o RSV as sociated lower respiratory infectio was relatively low (les than 5%), most RSV-related disease occurre in older children
Yamaoka et al. 2011 [68]	East Java	635	Pharyngeal swabs	influenza virus	influenza A(H3N3, pandemic H1N1 2009), influenza B	Patients ranging from all age groups.	Hospital based passive ILI surveillance study	Younge patients with milder symptoms were found t have pandemic (H1N1) 2009 viruses

Aditama et al. 2012 [69]	Throughout Indonesia	673	Serum, nasal and throat swabs	influenza A H5N1	influenza A H5N1	Children and adults from 0-30 years of age	Outbreak Investigation and disease transmission analysis	The ove household attack r was 18.3 and seconda attack r was 5.5 The me interval between onset of subsequ cases in outbrea was 5.6 days.
Agustiningsih et al. 2012 [70]	Throughout Indonesia	230	Nasal and throat swabs, tracheal aspirate, bronchoalveolar lavage	influenza A/H5N1	influenza A, enteroviru, human rhinoviru, CoV 229E/NL 63, HADV, BoV, parainfluenza virus -1,2,3, 4	Hospitalized suspected influenza H5N1 patients with ARI Children: 0-17 years of age Adults:15-60 years of age	NA	In child and adu bacteria infectio remain most commo etiologi acute respirat infectio althoug there w infectio caused viruses. Bacteri and vir co-infectio were identifie among adults a children

Prawira et al. 2012 [71]	Jakarta	321	NA	influenza A H5N1	influenza A H5N1	Hospitalized patients with influenza A H5N1 with median ages of 7 and 25 years of age for children and adults respectively,	NA	Patients usually developed rapid clinical deterioration and fatal outcomes. Deaths were mostly due to Acute Respiratory Distress Syndrome and usually occurred on day 7. Adults had a higher mortality rate
Kosasih et al. 2013 [13]	Sumatra, Java, Kalimantan, Bali, Lombok, Sulawesi, Maluku, Timor, Papua	21030	Nasal and throat swabs	influenza Virus	influenza A(H3N2,H1N1)v, influenza A H5N1, Influenza B	ILI patients with a median age of 17 years (mean age, 21.1 years; range, 1 month- 90 years of age)	Primary health centers and hospitals based passive ILI surveillance	Among outpatients and hospitalized patients influenza and B showed year-round circulation and were important causes of ILI.

Ikawati et al. 2014 [26]	Java	625	NA	NA	influenza A, influenza B, influenza A subtypes H1, H3, H5, pH1	Children between 0-5 years of age and adults >50 years of age	Passive ILI surveillance using National institute of health research and development (NHRD) data	ILI cases occurre most commonly in children aged 0- years old. Males tended to expe rience ILI more frequently than females ILI cases occur mostly among children aged 0- and 6-1 years old. The incidence of ILI droppe in 13– 17-year- olds bu increased again i the 18-34 age groups.
WHO et al. 2014 [72]	Throughout Indonesia	3	NA	influenza A H5N1	influenza A H5N1	NA	NA	NA

Pangesti et al. 2014 [20]	Throughout Indonesia	333	Serum, nasal and throat swabs	influenza virus	influenza A, H3, pH1, H5	Adults and children from all age groups	Hospital based passive SARI surveillance	Among the tota SARI cases the pro- portion of in- fluenza A was 5 % and in- fluenza B was 1%.
Zaman et al. 2014 [35]	Azerbaijan, Indonesia, Pakistan and Turkey	259	NA	influenza A H5N1	influenza A H5N1	Patients with possible or confirmed H5N1 infection with a median age of 17 years	Used data from inter- national patients registry for human cases of avain influenza	Confirm cases w more lik to have direct contact with another confirm case. U plained respirat illness, throat, excess sputum product and rhinorrh were mo frequen possible cases
Caini et al. 2015 [73]	Global	3653	NA	influenza virus	influenza A, influenza B	Outpatients and Inpatients	Passive surveil- lance, used data from national influenza centers of 43 countries.	Influenz co- circulat with influenz and account for roug 20% of total ca in all regions the wor

Farida et al. 2015 [74]	Semarang	148	Sputum, throat swabs, blood, sera, urine	viruses and bacteria	influenza A, influenza B, rhino virus, parain-fluenza virus, human coronavirus (HcoV OC43), adeno virus, human metapneu-movirus, RSV	Adult patients admitted with community acquired pneumonia with a median age of 58 years	Prospective cohort study	Viruses gram-negative bacilli a domina causes c commu acquire pneumo in Semara and Ce Java
Prasetyo et al.2015 [64]	Central Java	106	Nasal and throat swabs	respiratory viruses and torque teno viruses	influenza A H3, in-fluenza B virus, HMPV, HRV, adeno virus, human corona virus (HCoV-OC43), HPIV, TTV	Adult patients with ARI, ILI, or SARI ranging from 0-20 and >81 years of age	Hospital based passive ILI and SARI surveillance	First report of the circula-tion of HMPV, human aden-ovirus B, HCoV-OC43, and HPIV-3 in Indones
Storms et al. 2015 [21]	East Jakarta	5065	NA	influenza virus	influenza A (pan-demic (H1N1) 2009, H3), in-fluenza A H5N1, in-fluenza B	Outpatients with ILI and hos-pitalized patients with SARI in all age groups.	Hospital based passive ILI surveillance	34.5% o ILI cases and 15. % of SARI cases were tested positive for in-fluenza A,

Wertheim et al. 2015 [61]	Thailand, Vietnam and Indonesia	225 (Indonesia)	Nasal, and throat swabs, nasopharyngeal, and tracheal aspirates, nasal wash, bronchoalveolar lavage	viruses and bacteria	entero virus, rhinovirus, boca virus, RSV, para influenza virus -1,2,3,4 adenovirus, influenza A, and B, HMPV, coronavirus (HCoV-OC43), coronavirus e229, enteroviruses, paraecho virus,	Patients hospitalized with suspected influenza 0-5 and > 65 years of age	Passive surveillance from archived samples	In patie hospitali ized wit ILI, respirat viruses were th most commor detecte pathoge Rhinovi was the most frequen detecte virus account for 32% the patients whom v pathoge were detecte
Caini et al. 2016 [28]	Global	4231	NA	influenza virus	influenza A, influenza B	NA	Retrospective analysis of surveillance data (2000 -2014)	Reliable surveillance data is not yet available for many countries in the intertropical belt

Wiyatno et al 2016 [63]	Bandung	209	Preserved sera	coxsackievirus	coxsackievirus	Archived specimens available from non-dengue cases	Retrospective study from archived samples	The firs case of coxsack ievirus (CVB3) from an undiffer entiated febrile illness speci-men from Indones
Adam et al. 2017 [75]	Sumatra, Java, Kalimantan, Sulawesi, East Indonesia	334	Nasal and throat swabs	NA	influenza A, influenza B, RSV, rhinovirus adeno virus, enterovirus, parain-fluenza virus, bocavirus	ILI patients with a median age of 9 years	Hospital based passive ILI surveillance	The mo frequen combina tion of viruses identifie were adenovi and hu rhinovi
Haji et al. 2017 [32]	Global	175 (Indonesia)	NA	influenza A H5N1	influenza A H5N1	Individuals 0-16 and >63 years of age	Retrospective analysis of data reported to WHO (1997-2017)	Mortali in Indones due to H5N1 remaine high
Root et al. 2017 [27]	West Java	163014	Nasal and oropha-ryngeal swabs	influenza virus	influenza A (H3N2, H1N1 pdm09, H1N1), in-fluenza B	Patients between 0-5 years of age with ILI cases and symptoms	Hospital based passive in-fluenza surveillance	In rural Indone-sian house-holds with young children and poultry, there was an increase in in-fluenza A virus infectio

Amin et al. 2018 [76]	East Java	28,197	Oropharyngeal swabs	MERS-CoV	MERS-CoV	Returning Hajj Pilgrims with body temperature of > 38 °C accompanied by respiratory symptoms	Active surveillance	Absence infection due to MERS-CoV
Pawestri et al. 2018 [77]	24 Provinces of Indonesia	4752	Nasopharyngeal and oropharyngeal swabs	influenza virus	influenza A(H1N1 pdm09)	Patients with ILI and SARI	Hospital based passive ILI and SARI surveillance	Indicate the first occurre of oseltam resistan influenz (H1N1) viruses Indones
Susilarini et al. 2018 [10]	Yogyakarta, East Kalimantan, North Sumatera	1527	Respiratory specimens	influenza virus	Influenza A(H1N1 pdm09,H3N2), influenza B	Inpatients screening for SARI, in patients 0-4 and > 70 years of age.	Public health center and hospital based active SARI surveillance	The overall estimated annual incidence o influenz associat SARI ranged from 13-19 per 100 000 population Incidence was highest in children aged 0- years (82-114 per 100 000 populat

Wignjadiputro et al. 2018 [78]	North Sumatera, East Kalimantan, Yogyakarta, West Nusa Tenggara, North Sulawesi, Maluku	1806	Nasal and throat swabs	influenza virus	Influenza A(H3N2, H1N1)pdm09 and influenza B viruses.	Patients with SARI cases from 0-1 and [?]65 years of age.	Hospital based passive SARI surveillance study	Indones SARI surveil- lance system is flexible to incor porate surveil- lance fo other viruses
Wiyatno et al 2018 [62]	Jakarta	1	Serum, nasal swabs	rhinovirus C	rhinovirus C	4-year-old boy with increasing breathless- ness for a week	Case report	In a chi with ac onset of dilated cardiom opathy, there w possible associat of rhinovi C and myocar

Lafond et al. 2019 [22]	Jakarta	9819	Nasal and throat swabs	influenza virus	influenza A (H1N1 pdm09, H3N2), influenza A H5N1, influenza B	ILI case patients, SARI case patients between 0-5 or [?]65 years of age.	Public health centers based passive surveillance	31% of case-patients and 15% SARI ca patients tested positive influenz virus Influenz A(H1N influenz A(H3N and influenz virus infectio were detecte for 3 ye and the epidemi season extende from Novemb through May
Pawestri et al. 2019 [33]	15 provinces of Indonesia	180	Nasal, pharyn-geal, pleural, tracheal, bronchial, rectal, fecal, blood specimens	influenza A H5N1	influenza A H5N1	Patients with H5N1 infec-tion, from 1-67 years of age.	Retrospective study from clinical specimens	Of the 180 studied cases, 153 (85 %) were fatal. The case fatality rate in-creased from 73% in 2005 to 100% in 2012 and sub sequent years

Setianingsih et al. 2019 [23]	Jakarta	13	Sputum, oropharyngeal swabs, nasal swabs, nasopharyngeal swabs, and serum	MERS-CoV, alphavirus, flavivirus, paramyxovirus, herpes virus, henipa virus, hanta Virus, arenavirus and human metapneumovirus	influenza virus (H1N1,H3N2) enterovirus (EV D68, rhinovirus C, and A60) Coronavirus 229E, flavivirus, alphavirus, herpes simplex 1 virus, human metapneumovirus, dengue 3 virus	Hospitalized patients with suspected MERS-CoV infection.Majority of patients presented with pneumonia and symptoms of fever, dyspnea, and cough ranging from 32- 79 years of age	Observational study	The etiologic agents detected the sam were enterov D68, dengue virus ty 3, rhinovi C, HCo 229E, HSV-1, influenz virus H1N1, influenz virus H3N2, HMPV, and rhinovi A60
Anggraini et al. 2020 [48]	Surakarta	9	Blood, nasal and throat swabs	NA	SARS CoV-2	Pregnant women with SARS CoV-2 that were [?]20 years of age	Observational study	Pregnan women with neutrophil to lymphocyte ratio (NLR) of < 58 had a decreased risk of COVID 19

Asyary et al. 2020 [40]	Jakarta	NA	NA	NA	NA	Patients with SARS CoV-2	Cross sectional study	Higher duration of sunlight exposure was related to more cases of recovery from COVID-19 disease among patients
Burhan et al. 2020 [79]	Jakarta	3	NA	SARS CoV-2	SARS CoV-2	Patients with SARS CoV-2 47-year-old man	Case report	CT-Scan might be a better diagnostic tool compared to RT-PCR in diagnosing COVID-19

Gasem et al. 2020 [80]	Jakarta, Bandung, Yogyakarta, Semarang, Suryabaya, Bali, Makassar	1,486	Blood, nasal swabs, sputum, feces, urine	Pathogens causing febrile illness	NA	Children and adults [?]1 year of age, with body temperature of [?]38°C, and being hospitalized within the past 24 hours	Longitudinal cohort study	Indicate a lack o diagnosis of influenza in hospitals where most cases were diagnosed as nonspecific upper respiratory tract infections or pneumo
Gunadi et al. 2020 [54]	Yogyakarta	15	Nasopharyngeal swabs	SARS-CoV-2	SARS-CoV-2	Hospitalized patients with COVID-19 between 30 – 53 years of age	Observational study	SARS-CoV-2 with th D614G mutation appears to become the major circulating virus in Indones

Hafiz et al. 2020 [41]	Yogyakarta and Central Java	30	Nasopharyngeal swabs	SARS-CoV-2	SARS-CoV-2	Adult humans with SARS-CoV-2. 16 (53.3%) were male and 14 (46.6%) were female	Observational case series	Neutrop to-lympho ratio (NLR) and CXR are cost effective findings and can be used as a disease severity marker in primary health care to deter-mine further referral
Pitoyo et al. 2020 [42]	Jakarta	3	Serum, oropha-ryn-gealand na-sopha-ryngeal swabs	SARS-CoV-2, cytomegalovirus	cytomegalovirus	Adults above 60 years of age	Case report	Cytome infectio might be missed when depend-ing only on CT scans and radio-logical reports

Putra et al. 2020 [43]	Jakarta	1	Oropharyngeal and na-sopha-ryngeal swabs	SARS-CoV-2	SARS-CoV-2	29-year-old COVID with SARS-CoV-2	Case report	A COVID 19 patient reporte a pins and needles sensa-tion, and ex-foliatio of the skin on their hands
Ravindran et al. 2020 [81]	Bali	41	NA	SARS-CoV-2	SARS-CoV-2	The median age of cases was 31 years (range 3–64 years), which was similar to non-cases at 30 years (range 3–71 years)	Retrospective cohort study	Social gather-ings play im portant roles in trans-mission of COVID 19
Rozaliyani et al. 2020 [44]	Jakarta	4052	Nasal and pharyn-geal swabs	SARS-CoV-2	SARS-CoV-2	Participants' age range was 0-9 and 70 years of age. The mean age of the patients were 45.8 years	Retrospective cohort study	Older age, dysp-nea, pneu-monia, and pre existing hyper-tension were as-sociate with SARS-CoV-2 related deaths

Soedarsono et al. 2020 [49]	Surabaya, East Java	4	NA	SARS-CoV-2	SARS-CoV-2	Adults 34- 58 years old with SARS-CoV-2	Case studies	Infectio caused by SARS-CoV-2 can present with differen clinical manifes tations. Some patients that had no symp-toms initially devel-oped symp-toms later on

Somasetia et al. 2020 [50]	Bandung	1	NA	SARS-CoV-2	SARS-CoV-2	6-year-old male with SARS-CoV-2 infection	Case report	The patient was presented without classic upper respiratory symptoms of SARS-CoV-2, conjunctivitis, or rash and was instead presented with fever, acute abdominal pain, and shock

Tenda et al. 2020 [45]	Jakarta	3	Oropharyngeal andnasopharyngeal swabs	SARS-CoV-2	SARS-CoV-2	Older adults between 37- 57 years of age with SARS-CoV-2	Case studies	Fever was the most common symptom of SARS-CoV-2. Gastrointestinal symptoms in the form of diarrhea appeared in only one patient. Only one patient had dry cough

Widhidewi et al. 2020 [24]	Bali	200	Throat swabs	Family of paramyxoviridae, herpesviridae, coronaviridae, hantaviridae, adenoviridae, arenaviridae Genus of enterovirus, henipavirus, influenza A virus, bocavirus, Pneumovirinae viruses, Sub- family of RSV, human metapneumovirus	influenza A virus(H1N1, H1N2,), enterovirus 84, coxsackievirus A6, and A24, rhinovirus A, and C, coxsackievirus B3, human adenovirus B2, B3, and C measles D8, and parainfluenza virus 3, bocavirus, RSV A, B, human metapneumovirus, human coronavirus OC43, cytomegalovirus	Children and adults 0-6 and 80 years of age with acute respiratory tract infections	Cohort studies of children and adults with Acute respiratory infections	Positive detectio rate of respirat viruses 490 % T most commor viruses detecte were he pesviric enterov influenz and RS
Widysanto et al. 2020 [52]	Tangerang City	1	NA	SARS-CoV-2	SARS-CoV-2	48 year old male patient	Case report	Surviva with hypoxia in a critical COVID 19- positive ICU hospi- talized patient from Indones
Wirawan et al. 2020 [82]	Bali	NA	NA	SARS-CoV-2	SARS-CoV-2	NA	Modeling Study	NA

Yasmin et al. 2020 [51]	Bangdung	1	Nasopharyngeal and pharyngeal specimens	SARS-CoV-2	SARS-CoV-2	64-year-old female	Case report	Propose a syner-gistic concept of letha arrhyth mia due to direc SARS-CoV-2-associat cardiac injury, hyperin flamma-tory re-sponse, and drug-induced arrhyth
Aman et al. 2021 [25]	Bandung, Den-pasar, Jakarta, Makas-sar, Se-marang, Surabaya, and Yogyakarta	420	Blood, na-sopha-ryngeal swabs, sputum, urine, feces	influenza virus, RSV, chikun-gunya virus, measles virus, human coron-avirus OC-43, en-terovirus, herpes virus, human metapneumovirus	influenza, RSV, chikun-gunya virus, measles, human coron-avirus OC-43 en-terovirus, her-pesviri-deae virus, human metapneumovirus	Adults and children either 0-1 or [?]60 years of age with SARI	Hospital based passive SARI surveillance	Implem of the SARI criteria in tertiary referral hospi-tals would help identify poten-tial in-fluenza infectio

Baskara et al. 2021 [46]	Yogyakarta	1	Nasopharyngeal and oropharyngeal swabs	SARS-CoV-2	SARS-CoV-2	42 year old diabetic male with SARS-CoV-2	Case report	First case of COVID-19 disease with active primary tuberculosis in Indonesia. Limited or no protection against COVID-19 is one of the problems that leads to co-infection
Kadriyan et al. 2021 [53]	Nusa Tenggara Barat	2	Nasopharyngeal, and oropharyngeal swabs	SARS-CoV-2	SARS-CoV-2	26-year-old woman and 19-year-old man	Case report	The SARS-CoV2 gene remains detected in the tonsil and detritus even after the negative PCR report

Riawati et al. 2021 [47]	Yogyakarta	7	Nasopharyngeal and oropharyngeal swabs	SARS-CoV-2	SARS-CoV-2	Young and older adults (36- 71 years of age)	Case reports	Chest X-ray (CXR) is considered more effective and useful for initial screening and follow-up of the progress of patients with COVID 19

Figure Legend

Figure 1. Flow chart of the English language article search, review, and selection process.

Figure 2. Flow chart of the Indonesian language article search, review, and selection process.

Figure 3. Timeline of selected article publication by virus with notations of key respiratory virus outbreaks that have occurred in Indonesia since 1998.

Figure 4. Map of the study locations and population densities in Indonesia.