

Utilisation of Surveillance Data and Modelling Techniques to Inform Infectious Disease Control Programs in Indonesia

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Thesis submitted for the
Degree of Doctor of Philosophy

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Imperial College London
August 2023**

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Statement of Originality

I declare that the work presented here is my own work, conducted under the supervision of Dr Patrick Walker, Prof Thomas Churcher, and Dr Ellie Sherrard-Smith. All work carried out by others is appropriately referenced or described below. All sources used in the thesis have been cited appropriately. I wrote all the code used within the thesis except for the discretised Gamma distribution fitting, and SARS-CoV-2 transmission model fitting and scenario projections codes, which were written by Charlie Whittaker and Oliver J. Watson, respectively. I conducted the analysis and wrote the first draft of the thesis.

The works presented in **Chapters 2, 3, and 4** have been published in the following paper:

- **Djaafara, B.A.**, Whittaker, C., Watson, O.J., Verity, R., Brazeau, N.F., Widyastuti, Oktavia, D., Adrian, V., Salama, N., Bhatia, S., Nouvellet, P., Sherrard-Smith, E., Churcher, T.S., Surendra, H., Lina, R.N., Ekawati, L.L., Lestari, K.D., Andrianto, A., Thwaites, G., Baird, J.K., Ghani, A.C., Elyazar, I.R.F., and Walker, P.G.T. “Using syndromic measures of mortality to capture the dynamics of COVID-19 in Java, Indonesia, in the context of vaccination rollout.” BMC Med 19, 146 (2021). <https://doi.org/10.1186/s12916-021-02016-2>

In **Chapter 4**, Oliver J. Watson ran the model fitting process for the SARS-CoV-2 transmission model and the following scenario projections for each fitted model.

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August 2023

Abstract

Infectious diseases continue to pose a significant health challenge in Indonesia, despite progress in reducing their burden in the past decades. Furthermore, the emergence of COVID-19 in 2020 has further emphasised the pressing need for evidence-based policies and effective infectious disease control measures. To address this urgent need, this thesis utilises the combination of statistical and mathematical modelling approaches to analyse and explore disease surveillance data with the main objectives of enhancing our understanding of the current burden and transmission dynamics, evaluating the effectiveness of past interventions, and assessing the potential impact of future intervention strategies. This work focuses on two important diseases in Indonesia: COVID-19 and malaria.

This thesis' first three analysis chapters focus on analysing data related to the COVID-19 epidemic in Jakarta and Java Island. In **Chapter 2**, I utilised a branching process statistical model to estimate the effective reproduction number (R_t) of SARS-CoV-2 in Jakarta using various data sources, including the daily number of funerals with COVID-19 protocols (C19P), which accounts for people with COVID-19 symptoms who died without receiving COVID-19 tests. The results highlight that R_t estimates based on the C19P funeral data captured the earlier declines in COVID-19 transmission, which were also reflected by the Google community mobility data, and demonstrated a sustained decline in transmissibility throughout the period of strict non-pharmaceutical interventions (NPIs). Additionally, this analysis supports the hypothesis that COVID-19 was circulating before the first cases were detected in the country.

In **Chapter 3**, I developed a metapopulation model that took estimates of district-level population mobility from call detail records (CDR) data to evaluate the impact of NPIs implemented during the first wave of the COVID-19 epidemic in Java Island. The analysis found that the NPIs implemented not only helped curb the spread of COVID-19 from the urban epicentres in Java but also prevented a potentially larger disease burden in the rural areas where the populations are older, and healthcare is poorer.

In **Chapter 4**, I utilised an established mathematical model of COVID-19 dynamics, calibrating the model to the confirmed and suspected COVID-19 deaths data at the province level in Java Island. The model calibrations showed differences in the estimated current burden of the epidemic based on those two data, which led to differences in the future scenario simulations of the model. This emphasises the importance of choosing the correct data for model calibrations. Furthermore, the model simulations also demonstrated the importance of restricting transmission during the early period of COVID-19 vaccinations, highlighting the incremental impact of preventing people from getting infectious before receiving protection from the vaccines.

Transitioning to the analysis of malaria data, **Chapter 5** showed an analysis and exploration of routine malaria surveillance data in Indonesia from 2010 to 2019. The analysis explored the trends of multiple malaria metrics derived from the routine surveillance data, such as incidence rate, test positivity ratio, demography of malaria cases, and parasite species. By evaluating the context of those malaria metric trends observed, this chapter highlights the national-level success of the malaria control program in Indonesia, halving the total number of malaria incidences over the decade, with ongoing declines observed in most regions of the country. However, this analysis also showed how the progress towards malaria elimination has stagnated in the Papua region since 2015.

In **Chapter 6**, I used a plausibility design framework incorporating Bradford Hill criteria of causality to evaluate the hypothesis that the introduction of LLIN mass distribution campaigns was the main driver of the decline in malaria incidence across Indonesia from 2010 to 2019. By synthesising the evidence from the literature review, model simulations, and analysis of routine surveillance using the Bradford Hill causality criteria, I found strong evidence supporting the plausibility of LLIN mass campaigns as the main driver of malaria incidence declines across the country. This chapter also highlights the potential contribution of scale-ups of other interventions in maintaining the decline and preventing the resurgence of malaria incidence.

In **Chapter 7**, I conducted a high-resolution analysis of malaria data in Papua, the region contributing to the highest malaria burden in the country, where progress towards malaria elimination has plateaued. I developed a framework to calibrate the Imperial *Plasmodium falciparum* malaria mathematical model to malaria incidence data adjusted using the WHO case-adjustment formula at the district level. The modelling exercises highlight the variation in progress towards malaria elimination at both province and district levels, with stagnation and resurgence mainly driven by high-endemic baseline districts in Papua province. The analysis of LLIN distribution and usage data also revealed that lower utilisation of LLINs may have exacerbated the malaria problem in those districts.

Overall, this thesis demonstrates the value of integrating modelling techniques with disease surveillance data to further our understanding of disease burden and transmission dynamics in the population. It highlights the value of using alternative dataset, such as C19P funeral data, for estimating disease dynamics during the early phase of an epidemic when reporting and testing are still unreliable and limited. These are important findings for informing evidence-based policies for infectious disease control programs in Indonesia, with potential implications for other countries facing similar challenges.

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Acknowledgements

I am grateful for the kind and supportive people I have met and interacted with during my PhD journey. Their help, kindness, and encouragement have made this experience more enjoyable and rewarding.

Firstly, I want to express my deep gratitude to my primary supervisor, Patrick Walker. Your guidance, mentorship, advice, and patience have been instrumental in my success. Thank you for trusting me to pursue my interests and for your friendly banter that helped ease my anxiety. I am fortunate to have had you as my PhD supervisor. I would also like to extend my appreciation to my co-supervisors, Tom Churcher and Ellie Sherrard-Smith. Your wisdom and guidance have been invaluable, especially during the most challenging parts of my PhD. I am honoured to have had the opportunity to work with both of you.

So many members of DIDE and the MRC centre that I would like to thank for their help and kindness throughout this PhD journey. I want to thank Katherine, Ollie, Will, Helen, and Jonathan, my EECID cohort friends, who filled my days with laughter, especially during our MRes year. I want to thank Charlie and OJ for their encouragement, feedback, and friendship all these years. I want to also thank Charlie for his valuable feedback on my malaria chapters. I want to thank my office mates Daniela and Janetta. I want to thank the people in the malaria group: Nilani, Bob, Nick, Pete, Lucy, Isaac, Joseph, Sequoia, Richard, and Azra. I am grateful for all the help from the people in the Department: Anne, Natsuko, Christl, Sabine, Jeff, Pierre, Sangeeta, and Julie. Finally, I thank the Department for the funding.

I want to thank the Imperial Shorinji Kempo Family: Helena, Sensei Aled, Sensei Stu, Matteo, Ashleigh, Timur, Sensei Kavita, Vincent, Andy, Leah, Lidia, Kamila, Marie and others, for those lockdown trainings, online games, and punches, kicks, throws, etc. during our trainings.

I am also grateful to the Indonesian student community in the UK, who shares the same struggle for being far away from home. I extend the biggest and most heartfelt thanks to Mbak Fiona and Rizka. Looking forward to more Korean BBQs, anime song karaokes and bubble teas in the future. My housemate in this past 4.5 years, Rima, thank you for your friendship, kindness, and patience. I want to thank Laras for all the metal concerts we went to together. I want to thank my fellow OG Dota fan, Renard, who taught me to embrace gym life. Finally, I want to thank many Indonesian students and diaspora in the UK for their friendships over these years: Mas Imad, Dion, Mas Roni, Aurio, Yorga, Widya, Bang Ogie, Mbak Sandra, Kiky, Nisa, Aulia, Adhi, Atika, Teh Reynie, Fari, Mbak Shinta, Mbak Mona, Bang Nando, Inneke, Manda, Tika, Mbak Nida and Fahrin.

I want to thank Pak Desra, the Indonesian ambassador in the UK, for the many opportunities you gave me and other Indonesian students to help and support the embassy as best as we

could during the pandemic. In addition, I want to thank the Indonesian embassy in London staff: Bu Sayu, Pak Yoyok, and Pak AW.

My journey to epidemiological research started when I joined OUCRU in 2014. I want to thank Pak Iqbal, my mentor, who always trusts me and motivates me to pursue a PhD. I would also like to thank Karin, Rosa, Mas Adhi, Mas Henry, Mbak Lenny, Ihsan, Mas Rahmat, Kevin Baird, Guy, Mbak Ati, and Mbak Nunung.

I thank my collaborators at Indonesia NMCP: Bu Helen, Pak Guntur (alm.), Mbak Fajar, and Pak Asik; WHO Indonesia: Bu Herdiana; and Dinkes DKI Jakarta: Pak Verry, Bila, Ibu Dwi, dan Ibu Widyastuti. Thank you for all the opportunities and collaborations throughout these years.

There are many friends with whom I shared calls and video calls throughout lockdowns, which made life a lot easier to go through. They are Syifa, Bestari, Kak Liyana, Kak Ais, Desti, Aghni, Kak Vita, and Kak Randy. Thank you so much for the friendships.

I want to thank my family for all their love and support throughout these years. I thank my mom, Anita Djaafara, for all her love, prayers, and support. I thank my brother, Mas Bram, and Mbak Rara, for all their support. I want to thank Inong, our grandma, the source of cheerfulness in our family. Thank you, Tante Titi, my closest family in the UK, for always inviting me to have delicious Indonesian food at her place. Finally, I would like to thank the Suryometaram family, Pak Acong, Bu Ina, Satyo, and Opung, for all their love and support.

Finally, I want to thank my wife, Sasha, my sunshine. I am forever grateful to have you in my life. Thank you for your love, support, patience, understanding, encouragement, and all the time you've spent together with me, be it virtual or IRL :)

Chapter 1: Introductions

1.1 Background

1.1.1 An overview of Indonesia

Indonesia is the largest archipelagic country in the world, located at the equator ranging from 11°S to 6°N latitudes and 95°E to 141°E longitudes. There are more than 16,000 islands in the archipelago, with around 10% inhabited (Kementerian Dalam Negeri Republik Indonesia, 2022). Geographically, Indonesia comprises five large main islands (Sumatra, Java, Kalimantan/Borneo, Sulawesi, and New Guinea) and two groups of islands (Nusa Tenggara/Lesser Sunda and Maluku). Kalimantan Island is shared with Malaysia and Brunei Darussalam, while Timor and New Guinea Island are shared with Timor Leste and Papua New Guinea (PNG), respectively. Based on the recently passed laws on the proliferation of new provinces in the Papua region from two provinces to six provinces (Republik Indonesia, 2022a, 2022b, 2022c, 2022d), administratively, Indonesia comprises 38 provinces (admin level 1, the highest local government tier), 514 districts (admin level 2, which can be either a city or a regency/municipality), 7,904 sub-districts (admin level 3), and 83,467 villages (admin level 4) (Kementerian Dalam Negeri Republik Indonesia, 2019). However, for this thesis, I used the older administrative division from 2019, which divided the country into 34 provinces with the same number of districts, sub-districts, and villages (Kementerian Dalam Negeri Republik Indonesia, 2019).

Indonesia is the fourth most populated country in the world, with more than 270 million people, based on the most recent census in 2020 (Badan Pusat Statistik, 2021). Java Island is the most populated island in the country, and the world, with more than 151 million people living on the 128 thousand km² island (56% of the total population). Other main islands, such as Sumatra, Kalimantan, and Sulawesi, are also highly populated, with 58 million (22%), 16 million (6%), and 20 million people (7%), respectively. However, islands in eastern Indonesia, such as Maluku, Nusa Tenggara, and Papua, are less populated. These differences in population distributions are largely due to differences in economic development and activities; for example, Java Island and regions in western Indonesian, in general, are more urbanised and industrialised compared to the rest of the countries (G. Jones & Mulyana, 2015; Liu & Yamauchi, 2014). According to the most recent census by Statistics Indonesia (Badan Pusat Statistik/BPS) in 2020, Indonesia has a relatively young population, with a median age of 31 years old, and 65% of the population are under the age of 40 years old (Badan Pusat Statistik, 2021). Rural areas in Indonesia are relatively older than the urban ones, with the younger population moving to the rapidly growing urban cities and towns (Utomo et al., 2019).

The recent Global Burden of Disease (GBD) study assessing the subnational level of health burden in Indonesia showed a decline in infectious disease burden was observed from 1990 to 2019 (Mboi et al., 2022; Oktaria & Mahendradhata, 2022). However, over the same period, the country had been experiencing increases in the burden of non-communicable diseases (NCDs), such as ischaemic heart disease and diabetes, phenomena often called epidemiological transition. Recently, progress on communicable disease reductions has been slow, while the NCDs burden kept increasing in the population. The GBD study also revealed substantial health inequalities across provinces in the country. For example, provinces in western Indonesia have higher overall ranks across all health development indicators compared to the eastern region (Mboi et al., 2022; Suparmi et al., 2018). Addressing these inequalities represents an important challenge going forward.

Despite progress in reducing their burden in the past decades, infectious diseases are still an important health problem in Indonesia, especially for those living in the rural and poor regions of the country and the vulnerable populations such as children and the elderly (Kementerian Kesehatan Republik Indonesia, 2022). The 'big three' infectious diseases, human immunodeficiency virus infections and acquired immunodeficiency syndrome (HIV/AIDS), tuberculosis, and malaria remain significant health problems in the country (Kementerian Kesehatan Republik Indonesia, 2022). Additionally, neglected tropical diseases (NTDs) such as leprosy, yaws, dengue, rabies, lymphatic filariasis, schistosomiasis, and soil-transmitted helminths, are also still a huge problem, especially for the marginalised communities who are living in poverty (Wibawa & Satoto, 2016). Moreover, the emergence of COVID-19 in 2020 has further exacerbated the country's health problems, placing an enormous burden on the healthcare system and exposing vulnerable populations to an even higher risk of mortality (Surendra, Salama, et al., 2021). The challenges brought by the COVID-19 pandemic have further highlighted the urgent need for evidence-based policies to develop and implement effective control measures for health problems in Indonesia.

Healthcare is provided by the public and private sectors (Mahendradhata et al., 2017). The government provides primary health centres at the sub-district level and general public hospitals at the district and province levels, while private institutions provide private hospitals and clinics. In addition, through the Jaminan Kesehatan Nasional (JKN – universal health coverage) program, the government provides free or low-cost healthcare services to the public (Agustina et al., 2019). However, the access and quality of healthcare provided may vary widely across the country (Haemmerli et al., 2021; Wenang et al., 2021).

Infectious disease surveillance is conducted by the Ministry of Health and the health agencies under the provincial and district/municipal/city governments (Kementerian Kesehatan Republik Indonesia, 2014). Routine infectious disease surveillance activities (or indicator-based surveillance) are conducted at the health facilities level, with routine reporting to the district,

province, and national level within a certain period (i.e., daily, weekly, monthly, or yearly). This routine surveillance aims to analyse population disease patterns and risk factors, logistics management (i.e., vaccines, drugs, diagnostics), and outbreak preparedness. For rapid detection of outbreaks, Indonesia developed a national Early Warning Alert and Response System (EWARS) called *Sistem Kewaspadaan Dini dan Respon* (SKDR) in 2009. The system records weekly surveillance data for twenty-three diseases in Indonesia, with the primary data sourced from the primary health centres at the sub-district level. However, a recent study on the evaluation of this early detection system showed how disparities in reporting completeness and timeliness between the western and eastern regions of the country are also a problem in disease surveillance, despite improvements in the past few years (Hardhantyo et al., 2022). The gaps in human resources and infrastructures between these regions are reasons for these disparities.

1.1.2 COVID-19 pandemic

1.1.2.1 How COVID-19 unfolded globally

In December 2019, an outbreak of pneumonia with an unknown cause was found to be epidemiologically linked to a seafood and wet animal wholesale market in Wuhan, China (Wuhan Municipal Health Commission, 2019; Zhu et al., 2020). Later investigation identified the presence a novel coronavirus (2019-nCoV) in those pneumonia cases (Zhu et al., 2020). On 13th January 2020, the first imported case of 2019-nCoV, linked with international travel, was reported in Thailand (World Health Organization, 2020c). On 30th January 2020, the World Health Organization (WHO) Director-General declared the outbreak of the novel coronavirus a Public Health Emergency of International Concern (PHEIC) (World Health Organization, 2020e). By that time, there were 7,818 confirmed cases reported worldwide (World Health Organization, 2020b, p. 10). The majority of these cases were reported in China, with 82 cases reported in 18 countries outside China, some of them are Thailand, the Republic of Korea, the United States of America, Vietnam, and Singapore (Cuong et al., 2020; Holshue et al., 2020; Ministry of Health Singapore, 2020; Reuters, 2020a; World Health Organization, 2020c, 2020b). Later, the novel coronavirus was officially named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causing a disease called coronavirus disease (COVID-19) (World Health Organization, 2020d). Due to the alarming levels of spread and severity of the disease, WHO declared that COVID-19 could be characterised as a pandemic on 11th March 2020 (World Health Organization, 2020f).

1.1.2.2 COVID-19 in Indonesia and its impact

Local experts criticised the government's response to the unfolding pandemic due to the lack of testing capacity and efforts set up at that time (Rochmyaningsih, 2020). A statistical modelling study accounting for air travel volumes between Wuhan, China, to international

destinations with high connectivity to the city also showed that it was very likely that COVID-19 cases might have gone undetected in Indonesia (Salazar et al., 2020). On 2nd March 2020, the first confirmed COVID-19 cases in Indonesia were finally reported in Jakarta (Rochmyaningsih, 2020). An assessment done within the first month after the first cases of COVID-19 reported in the country showed that the country did not have the laboratory and human resource capacities to adequately perform population surveillance and tests at that time (Hendarwan et al., 2020). It was estimated that the assigned referral laboratories were only able to test, in total, 2,544 specimens per day, with 12 provinces did not have COVID-19 diagnostic laboratories (Hendarwan et al., 2020).

The emergence of COVID-19 in 2020 has significantly impacted many aspects of people's lives in Indonesia. The socioeconomic impacts of the COVID-19 pandemic in Indonesia have been severe (UNICEF et al., 2021), resulting in individuals' and households' loss of incomes and jobs, food insecurity, increasing poverty, and increased gender inequalities affecting women, among others (Samudra & Setyonaluri, 2020; UNICEF et al., 2021). COVID-19-related closures have also affected the education system, with over 60 million children in Indonesia experiencing significant learning losses (Butcher et al., 2021; Pradana & Syarifuddin, 2021; Yarrow & Afkar, 2021).

The pandemic has also had a devastating impact on public health in Indonesia. At least 160 thousand people, including at least 1,500 healthcare workers, have lost their lives to COVID-19 (Ekawati et al., 2022). The pandemic also further exacerbated the fragility of the country's healthcare system, as the overall system was strained and incapable of delivering essential healthcare services under prolonged emergencies (Mahendradhata et al., 2021). Furthermore, inequitable health impacts of the COVID-19 pandemic in the country were also highlighted due to unequal access to healthcare and inequality in the risk of COVID-19 infections in the population (Samudra & Setyonaluri, 2020).

1.1.2.3 Interventions and strategies during COVID-19 pandemic in Indonesia

Similar to other countries, at the initial phase of the pandemic, Indonesia relied on non-pharmaceutical interventions (NPIs) to slow the spread of the disease in the population. On 15th March 2020, President Joko Widodo held a press conference in response to the increasing number of COVID-19 cases reported. In the press conference, the President encouraged the people to social distance by working, studying, and worshipping at home and postponing activities involving a large number of participants (Cahya, 2020; WHO Indonesia, 2020). Less than a month later, on 10th April 2020, the national government implemented mandated social distancing measures, similar to lockdown, named *Pembatasan Sosial Berskala Besar* (PSBB – Large-Scale Social Restrictions) in the Greater Jakarta region before gradually increasing the coverage to other provinces (WHO Indonesia, 2020). Subsequently, a ban on domestic travel during the month of Ramadan from 24th April to 7th June 2020 was also implemented

(Ratcliffe & Firdaus, 2020; WHO Indonesia, 2020). In June 2020, some restrictions were eased and lifted, and Indonesia entered the *Adaptasi Kebiasaan Baru* (AKB) or the 'new normal' period, where restrictions were 'turned on' and 'off' according to the level of transmission in the population (WHO Indonesia, 2020). For example, PSBB was reimposed for four weeks in Jakarta due to the increased pressure on healthcare facilities in the city in mid-September 2020 (Widianto, 2020). In January 2021, Indonesia started its national vaccination campaign (Jiao & Aditya, 2021b; United Nations Office for the Coordination of Humanitarian Affairs (UN OCHA), 2021). The campaign initially targeted healthcare workers and then extended to target the elderly and public workers on 17th February 2021 (Cabinet Secretariat of the Republic of Indonesia, 2021a). In mid-2021, Indonesia faced its worst COVID-19 wave, with mortality surges as vaccination efforts for the general population continued (Lamb & Widianto, 2021). Currently, efforts for controlling COVID-19 focus on vaccinations, especially the booster dose, as the government revoked the policy imposing restrictions on community activities at the end of 2022 (Indonesia COVID-19 Task Force, 2022).

1.1.3 Malaria

1.1.3.1 Malaria as a disease of interest

Malaria is an acute febrile illness caused by protozoans in the genus *Plasmodium* (World Health Organization, 2022g). The disease spreads to humans through the bites of infected female *Anopheles* mosquitoes. There are currently five *Plasmodium* species causing malaria in humans: *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium malariae*, and *Plasmodium knowlesi*. *P. falciparum* and *P. vivax* are the two dominating malaria species across the globe, causing the greatest threat. *P. knowlesi* is found in Southeast Asia, originally known as malaria parasites infecting long-tailed and pig-tailed macaques. Malaria is a life-threatening disease. The common initial symptoms are fever, headache, and chills, which occur in the first 10-15 days after the infective mosquito bite. Those symptoms may be mild but can progress to severe illness and death if left untreated. Therefore, early diagnosis and treatment of malaria cases are key to reducing disease severity and transmission and preventing deaths. Parasite diagnostics are done through either microscopy or rapid diagnostics tests (RDT). The best available treatment for malaria currently is artemisinin-based combination therapy (ACT).

The life cycle of malaria parasites is shown in **Figure 1.1** (Centers for Disease Control and Prevention, 2020). The cycle starts when a female mosquito takes a blood meal from an infected human and then ingests the *Plasmodium* parasites (the gametocytes – sexual stage of malaria parasites) that are present in human blood. Within the mosquito, the *Plasmodium* gametocytes mate and develop into oocysts, which then mature and rupture, releasing sporozoites that migrate to the mosquito's salivary gland. This process typically takes 9 days or longer, a duration typically known as the Extrinsic Incubation Period (EIP), depending on

the parasite species and temperature (Ohm et al., 2018; Stopard et al., 2021). When the mosquito takes another blood meal from a human, it injects the sporozoites into their capillaries, which then make their way to the bloodstream. From there, the sporozoites will travel and infect human liver cells, resulting in the human liver stage of infection. In human liver cells, sporozoites mature and multiply into schizonts, which rupture and release merozoites. The merozoites will then infect red blood cells, starting the human blood stages of infection. They will multiply asexually and eventually burst out of the red blood cells, which could lead to typical malaria symptoms, such as fever and anaemia. Some of the parasites will then differentiate into the sexual stage of the parasite, gametocytes, waiting to be taken up by another mosquito having blood meals from the infected human, restarting the cycle. In *P. vivax* and *P. ovale* infections, a dormant stage of malaria parasites in the liver called hypnozoites can persist if untreated, causing relapses by releasing merozoites into the red blood cells weeks or even years later.

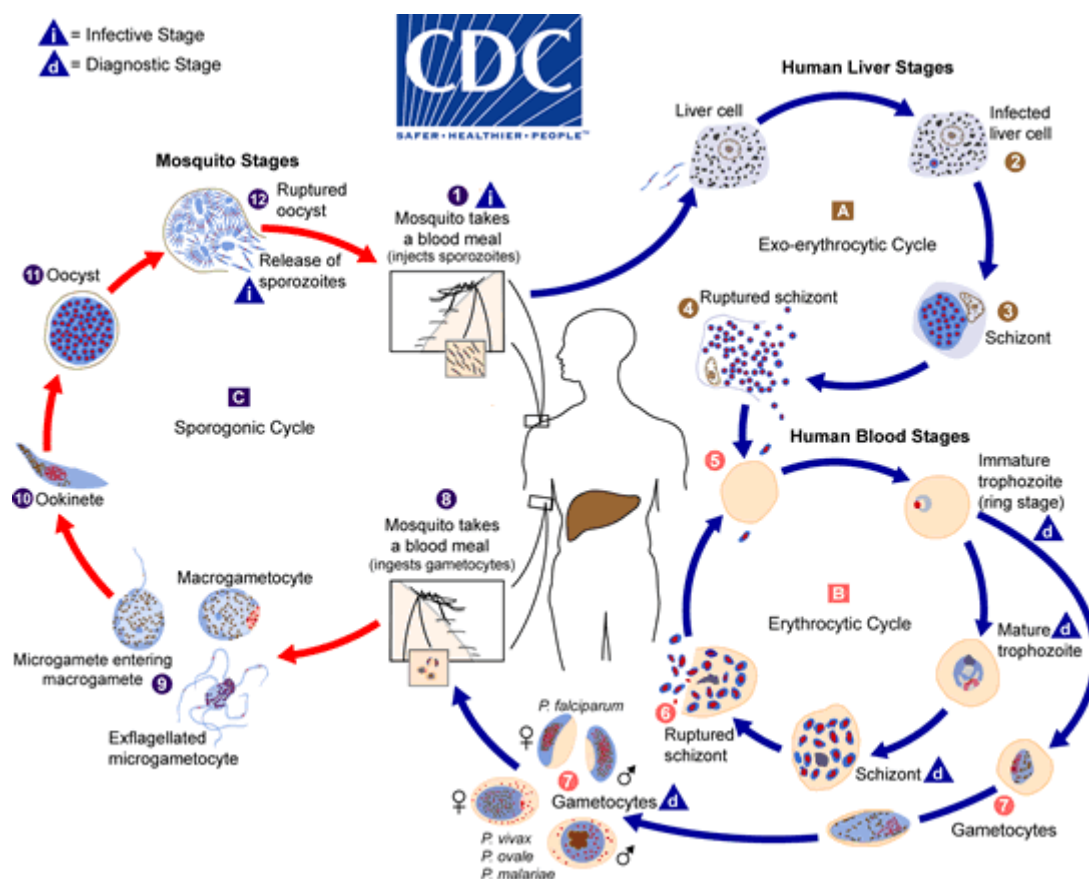


Figure 1.1. The malaria parasite life cycle. Cycle on the left with red arrows denote the mosquito stages of the cycle, while cycle on the right with blue arrows denote the human stages of the cycle, which include liver stages and blood stages. The figure was reproduced from the CDC website (Centers for Disease Control and Prevention, 2020).

Female mosquitoes need blood meals for egg production. After obtaining their blood meal, female *Anopheles* mosquitoes tend to rest while digesting the blood and developing their eggs. Once the eggs are fully developed, the female mosquitoes will lay them on a body of water. The eggs will then hatch, starting the aquatic stage of *Anopheles* mosquitoes, into larvae,

which then develop into pupae. The pupae then develop into adult flying mosquitoes. The detailed life cycle of *Anopheles* mosquitoes is shown in **Figure 1.2** (Centers for Disease Control and Prevention, 2022).

Many interventions have been developed to prevent malaria infections in humans, targeting various stages in the life cycles of malaria parasites and *Anopheles* mosquitoes. The intervention estimated to have contributed most to global declines in malaria burden in the 21st century is insecticide-treated nets (ITNs) (Bhatt et al., 2015), which provide protection through a barrier mechanism that prevents mosquitoes from biting the users and transmitting malaria, as well as through the insecticides that kill mosquitoes that come into contact with them. While users directly benefit from the protection provided by the nets, the whole community also receives indirect benefits from the reductions in mosquito populations and reduced survivorship beyond the EIP, which leads to reduced incidence of infections even in those who are not using a net (Hawley et al., 2003). This impact is often called the community effect. A recent modelling study found that the impact of the community effect protection of the nets is much higher than protections provided by the barrier effect (Unwin et al., 2023). In addition, indoor residual spraying (IRS) applies insecticide to house walls, targeting mosquitoes resting indoors after having their blood meals. ITNs and IRS are the core vector control interventions for malaria.

Early and accurate diagnosis is important for effective case management of malaria and for strong surveillance. For prompt diagnosis in the field, WHO recommends microscopy, which detects malaria parasites in blood samples, or rapid diagnostic tests (RDTs), which detect specific malaria antigens (World Health Organization, 2022b). Molecular detection capable of detecting low-density malaria infections is also available through nucleic acid amplification tests (NAATs), such as polymerase chain reaction (PCR) or loop-mediated isothermal amplification (LAMP) (World Health Organization, 2022c). However, they are currently only recommended for research purposes. The artemisinin-based combination therapies (ACTs) are the current first-line treatment for uncomplicated malaria in most countries (World Health Organization, 2018). This combination of drugs works synergistically with the artemisinin reducing the majority of malaria parasites quickly, and the partner drug clearing the remaining malaria parasites. In addition, to eliminate latent liver-stage infections and prevent relapse from infections of some malaria parasite species, such as *P. vivax*, a regimen of primaquine (PQ) is also included in a package of malaria treatment (World Health Organization, 2018).

Antimalarial drugs can also be taken prophylactically, and when applied at scale, this is typically referred to as chemoprevention (World Health Organization, 2022f). This approach aims to maintain drug concentration above the minimum concentration thresholds above which the parasite cannot complete its asexual blood-based cycle for a targeted period of time, such

as during a high-transmission season or in periods where individuals are particularly vulnerable to the consequences of infection such as infancy and pregnancy.

Finally, malaria vaccines currently under development and clinical trials also target different stages of malaria life cycles (Duffy & Patrick Gorres, 2020). For example, pre-erythrocytic vaccines (i.e., RTS,S vaccine) target sporozoite- or liver-stage parasites, transmission-blocking vaccines target sexual-stage parasites, and blood-stage vaccines aim to limit blood-stage parasite growth (Duffy & Patrick Gorres, 2020).

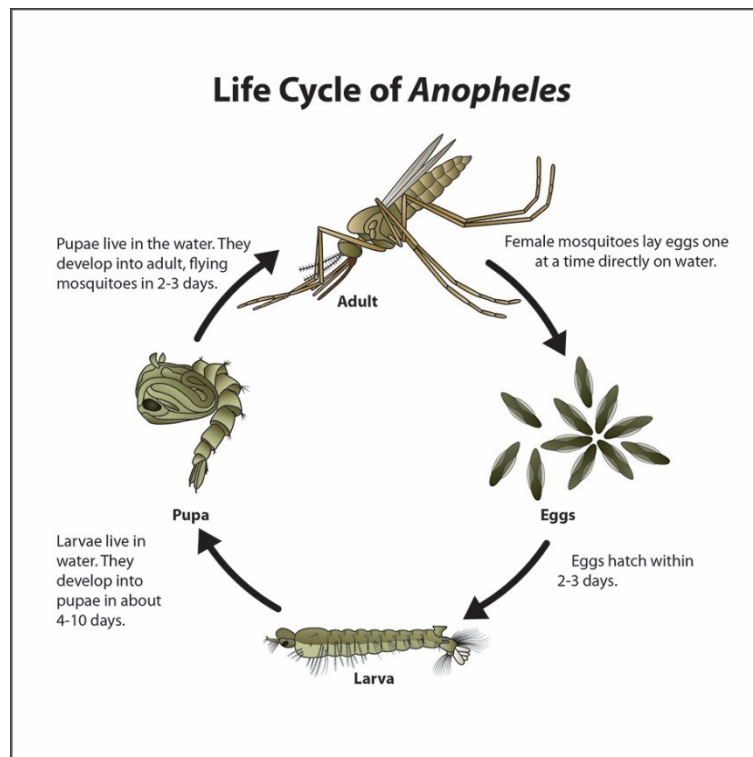


Figure 1.2. The Anopheles mosquito life cycle from the aquatic stages (eggs, larva, and pupa) to the adult mosquito stage. It usually takes 10-14 days for an egg to develop into an adult mosquito. The figure was reproduced from the CDC website (Centers for Disease Control and Prevention, 2022).

1.1.3.2 Global burden of malaria

Malaria is still a significant global health problem. The latest WHO malaria report estimated that there were 247 million malaria cases, causing 619 thousand deaths globally in 2021 (World Health Organization, 2022a). These figures have remained stable in the past few years, showing that efforts to eliminate and eradicate malaria have stagnated. The region contributing to the highest malaria burden in the world is Africa, driven largely by *P. falciparum*. The region was estimated to contribute around 95% of malaria cases and 96% of malaria deaths across the globe.

Furthermore, it is estimated that malaria contributes to around 7.8% of the deaths in children under the age of 5 years (World Health Organization, 2021b). The disease also has a significant impact on other sectors. For example, malaria is one of the main causes of school absenteeism in children (Brooker et al., 2000; King et al., 2015). Furthermore, it is also shown

that malaria impacts the economy significantly. Being ill from malaria reduces productivity and causes loss of income (Alaba & Alaba, 2009; Lukwa et al., 2019).

In Asia, malaria still has a significant impact, especially in countries with tropical climates. For example, India has the highest malaria burden in Asia (Wangdi et al., 2016; World Health Organization, 2022a). In Southeast Asia, Indonesia has the highest burden of malaria than other countries, mainly in the Papua region, the region neighbouring high-endemic Papua New Guinea, PNG (World Health Organization, 2022a). In other countries in Southeast Asia, especially in the greater Mekong region, efforts to eliminate malaria have stagnated mainly due to difficulties in managing malaria in the hard-to-reach populations (i.e., mobile and migrant populations) and treatment failures due to drug-resistant malaria parasites (Phyo & Nosten, 2018; Wangdi et al., 2021).

Overall, progress towards malaria eradication has stagnated in the past few years (World Health Organization, 2022a). Sustainable control efforts are key for progress towards malaria eradication (Birkholtz et al., 2012). However, control efforts have been hampered by issues such as insecticide resistance that reduces long-lasting insecticidal mosquito nets (LLINs) effectiveness, treatment failures due to the spread of drug-resistant malaria parasites, and false-negative RDT results due to, for example, the spread of parasites with *pfhrp2/3* gene deletions (Hemingway, 2018; Menard & Dondorp, 2017; Roberts, 2022; Watson, Sumner, et al., 2019). These highlight the importance of developing and adopting novel tools to help alleviate the mentioned problems and tackle the challenge from different directions (e.g., vaccines, radical cures, and gene-drive technology to modify mosquitoes) (Hemingway et al., 2016). However, it is also argued that sustainable progress for malaria elimination would not be achievable by only focusing on commodity-driven disease control. Addressing key weaknesses in the health systems, improving the quality and use of data for surveillance-response, improving malaria control leadership, and addressing multi-sectoral risk factors of malaria (i.e., housing, socio-economic) are also thought to be key to sustaining effective malaria control programs (Okumu et al., 2022).

Finally, declining funding to fight malaria has made it difficult for countries to scale up and sustain malaria control efforts (Rannan-Eliya, 2022). This problem was also exacerbated by the COVID-19 pandemic, which reduced funding for malaria control and disrupted countries' health services and malaria programs (Diptyanusa & Zablon, 2020). Therefore, in the next few years, there needs to be a renewed effort to create more sustainable funding to fight malaria in countries across the globe if the target to eradicate malaria remains on the agenda (Buguzi, 2022; Rannan-Eliya, 2022).

1.1.3.3 Malaria burden and control efforts in Indonesia

Malaria is still endemic in some regions of the country. Both *P. falciparum* and *P. vivax* are the dominant malaria parasites in the country. In 2017, Indonesia's National Malaria Control Program (NMCP) announced a significant milestone of 'eliminating' malaria in half of all districts across the country (Sitohang et al., 2018). Elimination means interruption of local malaria transmission within a district for three consecutive years. However, despite the significant milestone, progress towards malaria elimination has also stagnated in the past few years, especially in the eastern region of the country, where high-endemic malaria districts are mainly located.

Historically, malaria control efforts can be traced back to the Dutch colonial era in the early 1900s, where Swellengrebel used a technique called 'species sanitation', an environmental management and modification effort, as antilarval measures to reduce malaria prevalence mainly in Sumatra and Java (Takken et al., 1991). After declaring independence in 1945, the national government of Indonesia established the National Malaria Control Program, relying on dichloro-diphenyl-trichloroethane (DDT) spraying for vector control (I. R. F. Elyazar et al., 2011). In the 1960s, Indonesia altered its policy from control to elimination following the launching of the Global Malaria Eradication Program. However, due to the emergence of DDT-resistance mosquitoes across the country, financial constraints, and volatile political situations in the late 1960s, Indonesia reverted the national program to malaria control (I. R. F. Elyazar et al., 2011). After switching back to malaria control, control efforts were focused mainly on Java and Bali, where most economic activities occurred. As a result, malaria burdens were substantially reduced in these islands (I. R. F. Elyazar et al., 2011). In the early 2000s, the Rollback Malaria (RBM) campaign was initiated. Indonesia participated in the campaign by launching the 'Gebrak Malaria' campaign, which focuses on improving case detection, surveillance, and vector control activities. Finally, on 28th April 2009, the Ministry of Health of the Republic of Indonesia launched the national malaria elimination call (Departemen Kesehatan, 2009), aiming to eliminate malaria in the country by 2030. The malaria elimination targets were set in stages: 1) elimination in the thousand islands (Jakarta), Bali, and Batam islands by 2010; 2) elimination in Java, Aceh, and Riau islands by 2015; 3) elimination in Sumatra, West Nusa Tenggara, Kalimantan, and Sulawesi by 2020; and, finally 4) elimination in Papua, West Papua, East Nusa Tenggara, and Maluku islands by 2030.

1.1.3.4 Current malaria interventions and elimination strategies in Indonesia

After launching the national malaria elimination call in 2009, the Indonesian government renewed its intention to eliminate malaria. Malaria interventions and surveillance have been scaled up since the mid-2000s, showing major progress (Sitohang et al., 2018). Treatment with ACT was introduced in 2005, replacing chloroquine which had a major problem with drug resistance in the parasites at that time. Indonesia uses a combination of dihydroartemisinin-

piperaquine (DHP) and primaquine (PQ) to treat malaria cases. A longer regimen of PQ (14 days) is used to treat both *P. vivax* and *P. ovale* cases. LLINs were distributed through routine channels (i.e., antenatal care and under-5 years of age health checks) or mass distribution campaigns every three years that target high-endemic regions. Surveillance systems were improved through by developing reporting tools and improving diagnostic capacity (i.e., distribution of RDT kits and training of microscopists at the local health facilities). Finally, in low-endemic regions and regions already eliminating malaria in the country, proactive surveillance to detect imported cases was enhanced to prevent local malaria outbreaks.

1.1.4 Infectious disease surveillance in Indonesia

1.1.4.1 COVID-19 surveillance in Indonesia

Surveillance and reporting of COVID-19 in Indonesia during the initial phase of the pandemic were hampered by the country's limited ability to perform COVID-19 tests (van Empel et al., 2020). Some argue that the lack of testing capacity resulted from the government downplaying the severity of the unfolding pandemic (Djalante et al., 2020; van Empel et al., 2020). The first national COVID-19 testing protocol was published on 16 March 2020, two weeks after the first cases of COVID-19 were reported in the country (Kementerian Kesehatan Republik Indonesia, 2020). The protocol required all suspected COVID-19 cases specimens across the country to be sent to the government-owned COVID-19 referral laboratory in the capital city of Jakarta. This requirement caused significant delays (up to 10 days) in the lab confirmation of suspected COVID-19 cases due to the logistics and bottleneck created as the demand for tests largely surpassed the testing capacity of the referral laboratory (van Empel et al., 2020).

At the same time, experts and the public widely criticised the national government's lack of transparency regarding COVID-19 data reporting on their websites (Agahari, 2020; Januraga & Harjana, 2020; Pramiyanti et al., 2020). On top of that, the provincial and district governments also launched their own COVID-19 data reporting websites, providing information on the number of daily or cumulative COVID-19 cases and deaths in their provinces or districts (Agahari, 2020; Al Farizi & Harmawan, 2020). Information on the daily number of COVID-19 cases and deaths can be found from at least three governmental sources: 1) the National Disaster Management Agency website (which was later transferred to the national COVID-19 task force website); 2) the Ministry of Health website; and 3) provincial and district government websites. These multiple data reporting platforms became problematic as the numbers reported on the central government websites often differed from those provided by the local governments as their data were not integrated (Barsasella et al., 2022; Sutrisno, 2020). The lack of transparency and consistency in the government's COVID-19 reporting websites stimulated grassroots efforts from community groups of volunteers and civil society groups, such as KawalCOVID19 and LaporCOVID-19 (KawalCOVID19, 2020; LaporCovid-19, 2020), to launch their online spreadsheet and database of COVID-19 cases and deaths (Nadzir,

2020). These websites became popular as they combined multiple data sources from government websites, making comparisons easier.

Gradually, the Indonesian government improved and expanded its COVID-19 testing capacity (The Jakarta Post, 2020; Violleta, 2020). In addition, the successful integration and harmonisation of various data sources at different levels produced better quality information for the public and supported the government's policymaking during the pandemic (Aisyah et al., 2022; Krafft, 2022).

1.1.4.2 Malaria surveillance in Indonesia

One of the three pillars of the WHO's global technical strategy for malaria 2016-2030 is to 'transform malaria surveillance into a key intervention' (World Health Organization, 2021a). That means surveillance as an intervention should be able to monitor and measure not only the burden, transmission level, distribution, and determinant of malaria in the population but also the access, use, equity, and effectiveness of interventions implemented in the population. In Indonesia, the NMCP developed an electronic surveillance system to improve the validity and completeness of malaria data reporting called e-SISMAL (Elektronik Sistem Informasi Surveilans Malaria) (Subdirektorat Malaria Kementerian Kesehatan Republik Indonesia, 2018). This system was developed in 2010, initially using formatted and standardised Microsoft Excel files. However, as new indicators and data were needed to enhance the surveillance system as a key intervention for malaria elimination, e-SISMAL was updated in 2016 into an online web-based system.

e-SISMAL captures malaria program data up to the health facility level. The programmatic data the system captures are malaria suspect and positive case data from passive case detection (PCD) and active case detection (ACD), malaria treatment data, vector surveillance data, and vector control data. All the positive case data are recorded individually in the system. In contrast, data on suspects tested, logistics and vector-related programs are aggregated monthly.

Primary health centres at the sub-district level are responsible for reporting all data metrics. At the same time, the government's hospitals are only responsible for PCD-related data from people seeking care at the hospital. The health facility-level data are stored in Microsoft Excel files, which are uploaded periodically depending on the endemicity status of the districts where the health facilities are located (i.e., if the district-level Annual Parasite Incidence (API) per 1,000 > 5 data are uploaded monthly, API per 1,000 1-5: data uploaded weekly, and API per 1,000 < 1: data uploaded every time a new case is detected). If no cases were detected within a month, the health facilities still need to update logistics and vector-related data monthly.

District and provincial health offices can access the data from all the health facilities under their jurisdictions. However, they also have responsibilities to update logistic and programmatic data

to e-SISMAL. District health offices are responsible for updating logistics (i.e., drugs, diagnostics, LLINs, microscopes, etc.) stored in the district health office's warehouses, microscopists database, and cross-validation data for samples of malaria slides from health facilities. Provincial health offices are responsible for reporting on the availability of cross-checkers for malaria slides in each district and the stock of programmatic commodities stored in their warehouses. At the national level, the NMCP can access all the data uploaded to the e-SISMAL web server to monitor and develop national malaria elimination strategies based on the data provided.

1.1.5 Mathematical models in relation to COVID-19 and malaria

1.1.5.1 Mathematical modelling of infectious disease

A mathematical model of infectious disease refers to a set of equations used to describe how an infectious disease spreads in the population. This set of equations aims to represent the complex biology of the disease transmission process through mathematical representations of the underlying disease's natural history and ecology (Grassly & Fraser, 2008). Mathematical models are useful for understanding the dynamics of infectious disease transmission in the population as the transmission process accounts for the non-linearity due to the changes in disease prevalence and susceptible individuals over time (Garnett et al., 2011).

A common example of expressing transmission dynamics of infectious disease through a mathematical model is by using a compartmental model. Compartmental models simulate the dynamics of infectious disease at the population level. In compartmental models, the population under study is divided into compartments with assumptions on the 'disease state' of the population members (i.e., Susceptible, Infectious, Recovered) and the transition parameters between compartments (Brauer, 2008). These transition parameters represent the average rates of individuals transitioning between parameters. Finally, the rates of transfer between compartments are expressed mathematically as differential equations.

Another way to represent the transmission dynamics of infectious diseases is through an individual-based model (IBM). IBM allows tracking of every individual in the 'population' modelled and lets individual interactions within the model shape the population-level behaviours observed through the model output (Willem et al., 2017). However, IBMs are difficult to construct and analyse due to the substantial amount of information needed to establish model parameters that represent the behaviour of individuals (Garnett et al., 2011).

Furthermore, mathematical models of infectious disease can also be 'deterministic' or 'stochastic' depending on how they represent the role of chance in their models (Garnett et al., 2011). In a deterministic model, every realisation of the model is the same for a given set of parameter values. A deterministic model uses parameters that represent the average behaviour of the system and is usually useful to model the behaviour of systems with large

populations. However, deterministic models may give inappropriate results when chance and variability play important roles in the system. On the other hand, stochastic models simulate events happening to individuals based on chance. That means different results will occur when the model runs multiple times with the same parameters. This model is useful when the systems studied have small populations or when variability and chance play important roles in the systems. Stochastic models allow for variations due to chance to be quantified in their outcomes.

Finally, mathematical models should not be confused with statistical models (Garnett et al., 2011). Mathematical models offer a mechanistic representation of how the disease burden is established, which relies upon a good understanding of assumptions underlying the dynamics of transmission. In statistical models, the goals are usually to find patterns, estimate model parameters, or establish associations between variables of interest within the data available without any assumption on the transmission mechanisms. Hence, future predictions based on statistical models would depend on patterns seen in the data and the parameters established by the models. When used together in combinations, statistical models are used to estimate parameters of interest from empirical data, and mathematical models are used to make predictions based on those estimates of parameters (Garnett et al., 2011; Grassly & Fraser, 2008).

1.1.5.2 COVID-19 modelling efforts across the globe

Mathematical modelling played a critical role as one of the tools to provide evidence and advice regarding policy development and implementation during the pandemic (McBryde et al., 2020; Pagel & Yates, 2022). Over the time course of an epidemic, from the early emergence up to the late stage when the infection became endemic, modelling can be used to estimate key parameters of the epidemic (i.e., basic reproduction number, infection fatality ratio, the proportion of asymptomatic cases), evaluate the impact of interventions retrospectively, and explore future scenarios of the epidemic considering existing or novel interventions (Metcalf et al., 2020). Furthermore, SARS-CoV-2 models were developed at a multitude of complexities - accounting for clinical severity, immunology and vaccines, the emergence of new virus variants, and population behaviour, among other key aspects of transmission and disease risk - that were adopted as more data became available over the course of the pandemic (Davies, Barnard, et al., 2021; Davies et al., 2020; Knock et al., 2021; Sonabend et al., 2021). The models also developed at different geographical scales. There are efforts to specifically develop models to guide policies using country-specific models that were calibrated and parameterised to a plethora of data available in the country, as were done by several groups of academics in the UK (Brooks-Pollock et al., 2021). There are also efforts to provide a more general model that can be used to inform policies in low and middle-income countries (LMICs) (MRC Centre for Global Infectious Disease Analysis, 2020; van Zandvoort et al., 2020; Walker

et al., 2020). At the global scale, models were also developed to guide global vaccination distributions and prioritisations (Bubar et al., 2021; Hogan et al., 2021; Q. Li & Huang, 2022) and to evaluate key interventions during the pandemic such as quarantine policy for travellers (Quilty et al., 2021; Wells et al., 2022), for example. Finally, some models were also developed and used to account for the socioeconomic aspect of populations and to estimate their impact during the pandemic (Azzimonti et al., 2020; Baqaee et al., 2020; D. J. Haw et al., 2022).

1.1.5.3 Malaria modelling tools and software

The development of mathematical models of malaria can be traced back to the early 1900s when Sir Ronald Ross published a series of publications related to his studies on malaria transmission (Ross, 1915). Nowadays, there are many mathematical models of malaria already developed. Each of those models tries to account for complexities of malaria transmissions, such as different disease states in humans and mosquitoes, age-profile of infections, immunity, population migrations, environment, and interventions (both existing and novel), among others (Mandal et al., 2011; Smith et al., 2018). In addition, some of those models were developed as IBMs, allowing for discrete population simulations that may account for complex individual variations in humans, mosquitoes, or both, such as heterogeneities in individual disease progression and severity, and usage of mosquito nets (Smith et al., 2018).

Among all those mathematical models of malaria, some are further developed as modelling tools and software optimised to evaluate and explore scenarios related to malaria interventions in different settings. Some of those modelling software for malaria are: 1) EMOD malaria modelling from The Institute for Disease Modeling (Eckhoff & Wenger, 2016; The Institute for Disease Modeling, 2022); 2) OpenMalaria from Swiss Tropical and Public Health Institute (Golumbeanu et al., 2022; Swiss Tropical and Public Health Institute, 2015/2023); and 3) *malariasimulation* from Imperial College London (Charles et al., 2022; Griffin et al., 2010, 2014). All these modelling software share similarities in that they are IBMs, stochastic, parameterised to account for within-host dynamics and immunity, accounting for interactions with malaria interventions, and able to track important metrics such as morbidity and mortality.

1.1.5.4 Imperial College London *P. falciparum* malaria model

In this thesis, I used the Imperial College London *P. falciparum* malaria model implemented using the *malariasimulation* software package in R (Charles et al., 2022; Griffin et al., 2010, 2014). The original model has been used in various settings in Africa, with transmission and immunity parameters derived using data mostly from African settings, and mosquito parameters are derived based on the bionomics study conducted for each important mosquito species in Africa (*An. funestus*, *An. arabiensis*, *An. gambiae*). However, the model also has been used to help the PNG NMCP to design their control program. In addition, the *P. vivax* mathematical model (White et al., 2018), which is largely an extension of the Imperial malaria

model, adding the hypnozoite phase of the *P. vivax* transmission, also has been used in the PNG settings with adaptation on mosquito behaviour parameters based on the bionomics data collected for the important mosquito species in PNG (*An. punctulatus*, *An. farauti*, *An. koliensis*). Those models performed reasonably well in those exercises and studies and were validated. I chose the Imperial malaria model for my study in the Papua region of Indonesia due to its similarity to PNG regarding dominant vectors and ecology (Charles et al., 2022; Griffin et al., 2010, 2014).

In summary, the Imperial malaria model is a stochastic, individual-based model (IBM) for *P. falciparum* transmission dynamics that represents the human population as individuals, while the vector populations are represented as aggregates, stratified by species. The model incorporates the acquisition and loss of immunity to disease, detectable parasitaemia, and infection, accounting for the age profile of individuals and exposures to infections. The model also accounts for the heterogeneity in biting rates (Griffin et al., 2010, 2014). The full elaborations of each model component are available in **the Appendix**.

1.1.6 How modelling and surveillance intertwine to support policy

Modelling, in this thesis context, refers to collections of statistical modelling and mathematical modelling methods. Statistical modelling is useful for directly inferring parameters from the data that lead to important epidemiological information, such as the length of incubation and infectious periods. On the other hand, mathematical modelling, as defined in the previous section, refers to the description of the mechanistic process of disease transmission using mathematical notations (Heesterbeek et al., 2015).

Infectious disease dynamics are stochastic and highly nonlinear, resulting in counterintuitive phenomena that hinder extrapolation from one example to another. Therefore, modelling could provide a systematic tool to understand the spread of diseases in the population and inform effective ways to control them (Heesterbeek et al., 2015). Furthermore, with advancements in computing tools in recent years, sharing electronic data and developing complex mathematical models has become possible (Grassly & Fraser, 2008; Heesterbeek et al., 2015). This has led to an increased usage of surveillance data and modelling in informing policy for controlling and eliminating infectious diseases (Alahmadi et al., 2020; Grassly & Fraser, 2008).

However, challenges remain despite the increased usage and usefulness of both surveillance data and modelling for policymaking (Alahmadi et al., 2020). In the modelling part, the lack of identifiability of a model's parameters makes obtaining meaningful results and interpreting them challenging, which makes awareness related to this challenge important to ensure robust policy support from modelling exercises. In addition to the modelling application, it is also crucial to consider potential biases in the data, based on the situation (e.g., endemic or outbreak) and data types (e.g., routine surveillance or surveys). Explicitly defining the

observation process when parameterising a model with data is important to reduce bias, but the data quality can still impact precision. Acknowledging and communicating the limitations of the model, data, and their results are crucial, particularly when the results are intended to inform policy. Therefore, it is important to carefully examine and address potential biases and limitations when using modelling and surveillance data for decision-making purposes (Alahmadi et al., 2020).

1.2 Research gap and rationale

1.2.1 Background

My PhD thesis originally focused on modelling and analysing malaria surveillance data in Indonesia. However, the COVID-19 pandemic hit the world in 2020, presenting some interesting scientific questions at the time that can also be used to inform policy. Hence, I led an analysis related to surveillance data and modelling of COVID-19 in Indonesia in collaboration with the Jakarta Provincial Health Office and Oxford University Clinical Research Unit (OUCRU) in Indonesia, which became half of my thesis content. I then returned to the original research proposal on malaria. Though involving two distinct disease contexts, the analyses share similar themes, particularly on leveraging multiple metrics to facilitate the interpretation of disease surveillance data and their integration within modelling analyses attempting to inform policy.

1.2.2 COVID-19

During the early phase of the COVID-19 pandemic, many low- and middle-income countries (LMICs) faced major challenges in accessing diagnostic tests and increasing their testing capacity for detecting SARS-CoV-2 infections. As a result, measuring the true extent of the outbreak, including transmission intensity and disease burden, became difficult, hindering effective responses from policymakers and the public. Therefore, alternative methods for measuring transmission or disease burden were needed to overcome these data gaps. These alternative methods could include utilising alternative datasets with less bias than the reported cases and deaths when testing capacity was limited or developing new methods that could address those biases. Moreover, evaluations of the impact of interventions implemented during the pandemic on reducing cases and deaths are necessary. However, the unavailability of high-quality data made it difficult to perform such evaluations. In Jakarta, burials data, specifically burials with COVID-19 protocols (C19P) performed for the confirmed COVID-19 deaths or suspected COVID-19 cases who died before receiving their diagnostic results, represents an example of such an alternative data source. The research gap lies in analysing whether this dataset may provide a more accurate picture of the outbreak and aid in effective policymaking and response. Mathematical models can be useful tools for evaluating

intervention impacts given outcomes from the different data, providing valuable insights for future pandemic strategies.

1.2.3 Malaria

Indonesia's goal to eliminate malaria by 2030 has faced stagnation in recent years despite the intensification of efforts, especially in the past decade. While the Indonesia NMCP has improved the quality and availability of malaria surveillance data collection, there have been no formal assessments on the impact of intensified interventions across the country. Given the heterogeneous malaria landscape of the country, this analysis is crucial for future intervention planning. Mathematical modelling can support malaria control and elimination programs but is rarely used in Indonesia. With limited control tools and budget constraints, modelling can inform future control policies, including introducing new intervention tools and optimising control strategies given the available budget. However, mathematical models need to be parameterised and calibrated with local data. Given the limited amount of 'gold standard' data for malaria model calibration, i.e., prevalence survey data, there needs to be a framework to calibrate mathematical models using routine surveillance data.

1.3 Aims

The thesis aims to address research gaps in understanding COVID-19 and malaria transmission in Indonesia, combining surveillance data and modelling techniques. The first three analysis chapters (**Chapters 2, 3, and 4**) focus on COVID-19, and the final three (**Chapters 5, 6, and 7**) focus on malaria. The aim of each chapter is to:

1. Use an alternative dataset to estimate the SARS-CoV-2 transmission intensity in Jakarta (**Chapter 2**)
2. Develop a metapopulation model to estimate the potential impact of COVID-19 spread in Java Island (**Chapter 3**)
3. Use mathematical models combined with an alternative dataset to estimate the current burden of COVID-19 in Java Island and project future scenarios of transmission in the context of the upcoming national vaccination rollouts (**Chapter 4**)
4. Analyse and explore the trends of malaria surveillance metrics from routine surveillance data in Indonesia from 2010 to 2019 (**Chapter 5**)
5. Use a plausibility design framework incorporating causality criteria to assess the plausible impact of LLIN mass distribution campaigns in Indonesia (**Chapter 6**)
6. Develop a framework to calibrate a mathematical model of *P. falciparum* malaria using routine surveillance data (**Chapter 7**)

The thesis will end with a discussion and conclusion chapter, summarising all the findings, their limitations, and future research plans.

Chapter 2: Using a syndromic measure of mortality to infer transmission dynamics and burden of COVID-19 in Jakarta, Indonesia

In **Chapters 2, 3, and 4**, the analyses focus on the COVID-19 transmission dynamics and mathematical modelling in Indonesia. The region of focus of the analysis was Java Island, the country's most populated island and the first epicentre of the COVID-19 pandemic in Indonesia. The results in these chapters were already published in BMC Medicine on 18th June 2021 in a paper titled 'Using syndromic measures of mortality to capture the dynamics of COVID-19 in Java, Indonesia, in the context of vaccination rollout' (Djaafara et al., 2021). This chapter focuses on how the pandemic unfolded in the capital city, Jakarta, and how it subsequently spread through the population. As testing capacity was very limited at the beginning of the pandemic, there were concerns that conventional epidemiological surveillance data for COVID-19, such as cases and deaths, might be unreliable in tracking the trajectory of the transmission in the population. Therefore, I explored an alternative dataset, the daily number of funerals with COVID-19 protocols recorded by the Jakarta Department of Health, to see whether it would provide a better view of how the pandemic unfolded in the population, especially during the first year of the pandemic within the city.

2.1 Introductions

2.1.1 Background

An outbreak of cases of pneumonia with unknown causes was reported on 31st December 2019 in the city of Wuhan, China, by the World Health Organization (World Health Organization, 2020g). Further investigations concluded that a novel coronavirus (2019-nCoV) was identified as the disease's causative agent. The virus was subsequently named the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes a disease called coronavirus disease 2019 (COVID-19) (World Health Organization, 2020d). The disease may vary in severity as it may cause only asymptomatic or mild illness to life-threatening conditions requiring intensive care (Verity et al., 2020). As of 13th December 2022, more than 645 million confirmed COVID-19 cases and more than 6 million COVID-19 deaths were reported globally (World Health Organization, 2022d).

In 2020, vaccine candidates and effective treatments were still under development and under extensive global clinical trials to test their efficacy and effectiveness in preventing and treating the disease (Ball, 2020; P. S. Kim et al., 2020; Wilkinson, 2020; World Health Organization, 2020a). At that time, country governments across the world relied on non-pharmaceutical interventions (NPIs) such as border restrictions, local quarantine, social distancing, tracing and

tracking, and extensive isolations of confirmed and suspected cases to control and prevent the local transmission of the virus (Haug et al., 2020). However, implementations of NPIs also created a huge dilemma as the measures are associated with high socioeconomic costs (Skarp et al., 2021). Subsequently, some countries were able to bring the disease under control and reduce the daily case and death counts after an extensive period of NPIs implementation (Flaxman et al., 2020a). They subsequently gradually lifted the restrictions to embrace the period of the 'new normal' (Heavey & Balmer, 2020; Lacina, 2020).

As of 13th December 2022, Indonesia reported the second-highest number of confirmed COVID-19 cases among Southeast Asian countries, with more than 6.7 million cases reported. The number was almost half the reported number of confirmed COVID-19 cases in Vietnam, which reached 11.5 million cases. However, Indonesia reported more than triple the confirmed COVID-19 deaths, the highest in Southeast Asia with more than 160 thousand deaths, compared to reported COVID-19 deaths in Vietnam (World Health Organization, 2022d). Cases were first reported in West Java province, on the island of Java, on 2nd March 2020, amid concern that the disease had circulated widely before (Rochmyaningsih, 2020; Salazar et al., 2020). The city of Jakarta (the capital of Indonesia, also known as the Jakarta province) subsequently became the epicentre of the country's COVID-19 epidemic, following which the disease spread throughout the island.

Like in other countries, NPIs were the main interventions implemented by the national government to curb the spread of COVID-19 in the population throughout 2020 (WHO Indonesia, 2020). NPIs implemented included national social distancing measures encouraging people to work, study, and worship at home (15th March 2020); mandated social distancing measures implemented on 10th April 2020 as part of a lockdown, named *Pembatasan Sosial Berskala Besar* or PSBB in Indonesian; and a ban on domestic travel during the holy month of Ramadan (24th April to 7th June 2020) (Rayda, 2020). However, in June 2020, Indonesia entered the *Adaptasi Kebiasaan Baru* (AKB or 'new normal') period, where some restrictions were lifted (WHO Indonesia, 2020). During this AKB period, the reported incidence of COVID-19 cases and deaths increased across Indonesia, with community transmission evident across the six provinces of Java. Subsequently, PSBB was reimposed in mid-September for four weeks in Jakarta in response to pressures on healthcare facilities across the city (Widianto, 2020).

Understanding the trajectory of the epidemic in Jakarta was challenging. As in many countries, testing constraints in Indonesia have limited the extent to which officially confirmed cases reflect underlying trends (Burki, 2020; Watson et al., 2021). Similar concerns exist for mortality data based on the high numbers of individuals exhibiting COVID-19-like symptoms who died before receiving a diagnosis (Spiegelhalter, 2020; Syakriah, 2020a). In Jakarta, such individuals (and similarly those who died after testing positive for COVID-19) are buried under

strict COVID-19 protocols (C19P). Burial workers preparing the C19P funerals must wear personal protective equipment, while the deceased bodies are wrapped in plastic and placed inside a coffin (Gugus Tugas Percepatan Penanganan COVID-19, 2020). This syndromic measure of mortality could potentially become very useful to fill in the gap in the lack of quality surveillance systems and reporting, especially in the early phase of the epidemic.

2.1.2 Aims

In this chapter, the analyses focused on the dynamics of the COVID-19 spread in Jakarta, the capital of Indonesia, which became the country's largest epicentre of the epidemic. I aimed to:

1. Estimate the effective reproduction number over time (R_t) of the SARS-CoV-2 infections in Jakarta using the COVID-19 surveillance data collected by the Jakarta Department of Health, including the number of burials with COVID-19 protocols (C19P).
2. Measure the relationship between virus transmissibility and changes in population mobility in Jakarta throughout the observed epidemic in the city.

2.2 Data and methods

2.2.1 Data

2.2.1.1 Epidemiological data

Epidemiological data for the Jakarta province were obtained from the official Jakarta COVID-19 data monitoring website: <https://corona.jakarta.go.id/id/data-pemantauan> (Jakarta Provincial Health Department, 2020). This website provided the daily reported cases, reported deaths, funerals with COVID-19 protocol (C19P), and tests conducted with their daily positivity ratio. However, COVID-19 cases and deaths are typically subject to varying degrees of reporting delays, with no available data on the date of diagnosis or death (van Empel et al., 2020). The daily C19P funerals, on the other hand, represent the daily number of burials conducted on the reporting day. Such protocols are observed during the funerals of both confirmed COVID-19 cases and those individuals suspected of having COVID-19, where mortality occurred prior to receiving a confirmatory diagnosis. Hence, the C19P funerals data represent a measure of mortality in suspected and confirmed COVID-19 cases. For this analysis, data were collated up to 7th December 2020.

Anonymous individual data of 11,280 confirmed COVID-19 cases up to 29th June 2020 in Jakarta were obtained from the Jakarta Department of Health (Surendra, Elyazar, et al., 2021). Data comprise dates of onset of symptoms, attendance in the hospital, and deaths.

2.2.1.2 Province-level changes in population mobility

The province-level mobility changes data were acquired from the freely-available Google COVID-19 Community Mobility Reports, which can be accessed at: <https://www.google.com/covid19/mobility/> (Google LLC, 2020). The data comprise changes in the population mobility compared to the baseline level on six place categories: grocery and pharmacy, parks, transit stations, retail and recreation, residential, and workplaces. The baseline value for each category is the median value, for each corresponding day of the week, during the first five weeks of early 2020 (3rd January to 6th February 2020). Changes in the population mobility of Jakarta up to 7th December 2020 were used for the analysis.

2.2.2 Methods

2.2.2.1 Estimating delay distributions of onset of symptoms to diagnosis and onset of symptoms to death

The distributions of the onset of symptoms to diagnosis (onset-to-diagnosis) and the onset of symptoms to death (onset-to-death) of confirmed COVID-19 cases were estimated from individual patient data obtained from the Jakarta Department of Health (Surendra, Elyazar, et al., 2021). Due to the discrete nature of the observed data on those delays (measured in days), I used the discretised Gamma distribution (dy) with two parameters, k and θ , as its shape and scale parameters, respectively (Chakraborty & Chakravarty, 2012), to estimate the distributions of those delays. Chakraborty & Chakravarty showed how the discretised Gamma distribution could provide good fitting to under and over-dispersed discrete survival data (Chakraborty & Chakravarty, 2012). The fitting process for the onset-to-diagnosis and onset-to-death delays was done using `rstan` (Stan Development Team, 2020) in R. Data on delays between the onset of symptoms and hospitalisation were used for the fitting process of onset-to-diagnosis distribution, as COVID-19 patients in 2020 were tested on the day they were hospitalised.

2.2.2.2 COVID-19 cases and deaths reconstruction to onset dates

The daily reported cases, deaths, and C19P funerals data in Jakarta were reconstructed to represent the day of symptom onset of each reported event. The reconstructions were based on the estimates of the delay distributions between onset-to-diagnosis and onset-to-death. In addition, each C19P funeral was assumed to occur the day following the date of death. So, an additional one-day delay was added for the C19P funerals data.

Case data delays were based on the onset-to-diagnosis delay distribution, while death and funeral delays were based on the onset-to-death delay distribution. For each reported event, uncertainty in the lengths of delays were represented by drawing 100 times from the relevant delay distributions of onset-to-diagnosis or onset-to-death. Based on those draws, 100 sets of reconstructed daily frequencies of the onset days of cases ($I_{t,cases}$), deaths ($I_{t,death}$), and

funerals ($I_{t,funeral}$) were calculated. Finally, adjustment for the right censoring occurring due to individuals with symptoms who have yet to reach the outcome was also carried out. These adjustments were made by dividing the inferred onset frequency on a given day by the cumulative probability it would have been observed by the last date within the dataset, based on the estimated parameters of Gamma distributions of onset-to-diagnosis and onset-to-death. The cumulative probability of Gamma distribution is as follows:

$$F(x; \alpha, \beta) = \frac{\gamma(\alpha, \beta x)}{\Gamma(\alpha)}$$

where $\gamma(s, x)$ is the lower incomplete Gamma function:

$$\gamma(s, x) = \int_0^x t^{s-1} \exp(-t) dt$$

and x is the value of the random variable X , which in this case, is the number of days before the last reporting date in the data. Hence, the reconstructed daily onset frequencies of the onset day of cases adjusted for right censoring ($I'_{t,cases}$), for day x (where $x = 0$ means adjustment for the last reporting date of the data) is formulated as:

$$I'_{T-x,cases} = \frac{I'_{T-x,cases}}{F(x; \alpha, \beta)}$$

where T is the last reporting date of the data.

2.2.2.3 Estimating SARS-CoV-2 transmissibility over time in Jakarta

SARS-CoV-2 transmissibility over time in Jakarta was estimated in terms of the daily effective reproduction number (R_t). R_t represents the average number of new infections caused by a single infectious individual, accounting for population immunity, changes in human behaviours, and policies that might affect transmission (Gostic et al., 2020). The daily reported number of COVID-19 cases, deaths, and funerals with COVID-19 protocols (C19P) were used to estimate the R_t , respectively labelled as $R_{t,cases}$, $R_{t,deaths}$, and $R_{t,funeral}$ for estimates from each data source. There were two steps in assessing the transmissibility of the virus based on the mentioned datasets:

- 1) Reconstruction of the reported event data to represent the day of onset of each reported event as explained in 2.2.2.2; and
- 2) Estimation of R_t based on the reconstructed onset days data.

The daily effective reproduction number (R_t) can be estimated by calculating the ratio between the number of infections at time t (I_t) and the total infectiousness of infected individuals at time t (λ_t). Furthermore, the total infectiousness of individuals (λ_t) can be mathematically described using a renewal equation (Cori et al., 2013; Fraser, 2007):

$$\lambda_t = \sum_{s=1}^t I_{t-s} \omega_s,$$

where ω_s is the infectivity profile of an infected individual at the time s after the symptom onset, the distribution of which is approximated by the serial interval distribution. The transmission was modelled as a Poisson process:

$$I_t \sim \text{Poisson}(R_t \lambda_t).$$

The `EpiEstim` package (Cori et al., 2013, 2020) in R was used to implement the mathematical estimate of the SARS-CoV-2 R_t in Jakarta for each reconstructed case ($R_{t,cases}$), death ($R_{t,death}$), and C19P funeral ($R_{t,funerals}$) data. R_t at the beginning of the epidemic was estimated for the period before 2nd March 2020 (when the country's initial COVID-19 cases were announced). Subsequently, R_t was estimated over a weekly sliding window, with the mean and standard deviation of the serial interval distribution were assumed to be 6.3 and 4.2 days, respectively (Bi et al., 2020a).

2.2.2.3 Measuring the relationship between SARS-CoV-2 transmissibility and daily mobility changes

1,000 random samples were drawn from the posterior samples of the estimated $R_{t,cases}$, $R_{t,death}$, and $R_{t,funeral}$ at each time point. Then, the daily average changes in non-residential population mobility, accounting for all place categories in the Google Community Mobility Report except residential mobility, were calculated. Pearson's correlation coefficients for R_t estimates based on the case, death, and funeral data were calculated against the daily average changes in non-residential mobility in Jakarta based on Google mobility estimates.

2.3 Results

Figure 2.1 shows the model fitting to estimate the distribution of the onset of symptoms to hospitalisation and the onset of symptoms to death delays. The mean estimate of the onset-to-diagnosis delay (represented by the onset-to-hospitalisation delay) was 7.62 days, with a standard deviation of 7.51 days. The mean estimate of the onset-to-death delay was 15.87 days, with a standard deviation of 9.34 days.

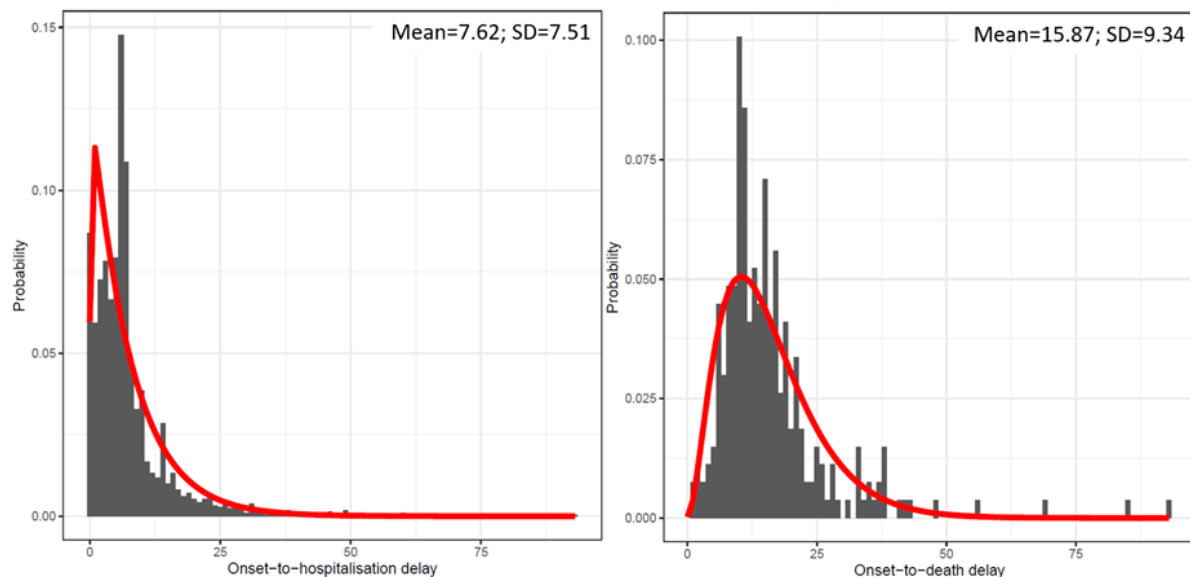


Figure 2.1. Discretised Gamma distribution fittings to onset-to-hospitalisation delay data (left) and onset-to-death delay data (right).

Figure 2.2A shows the temporal trends of the daily reported confirmed COVID-19 cases, confirmed COVID-19 deaths, C19P funerals, and test positivity ratios (the proportion of positive tests). The number of reported cases during the second peak was far higher than the first. However, the test positivity ratios were relatively high during the initial phase of the epidemic before declining in the first half of 2020, likely indicating increased testing rates and case ascertainment. Furthermore, all three metrics showed declining or stagnating trends during the period of PSBB (the light green shade areas). However, there were differences in the timing of changes in trends of each of those metrics. For example, in the early phase of the pandemic in Jakarta, the declining trend in the metric trajectory was observed earlier in the C19P funerals data compared to other metrics.

The three surveillance metrics were then transformed into inferred symptom onset dates (**Figure 2.2B**). It is estimated that 31 (22-41, 95% Credible Interval/CrI) and 124 (107-139, 95% CrI) confirmed COVID-19 deaths and C19P funerals (assuming all funerals represent deaths due to COVID-19) had symptom onset occurring before 2nd March 2020, when COVID-19 was first identified in Indonesia. Furthermore, assuming an infection fatality rate by Verity et al. (Verity et al., 2020) and Jakarta population age structure, it is also estimated that 10,950 (7,530-14,040, 95% CrI) infections based on confirmed COVID-19 deaths or 42,100 (36,280-47,570, 95% CrI) based on C19P funerals (reflecting an assumption that all undiagnosed individuals provided with C19P funerals would have tested positive) had occurred cumulatively in Jakarta by 2nd March 2020.

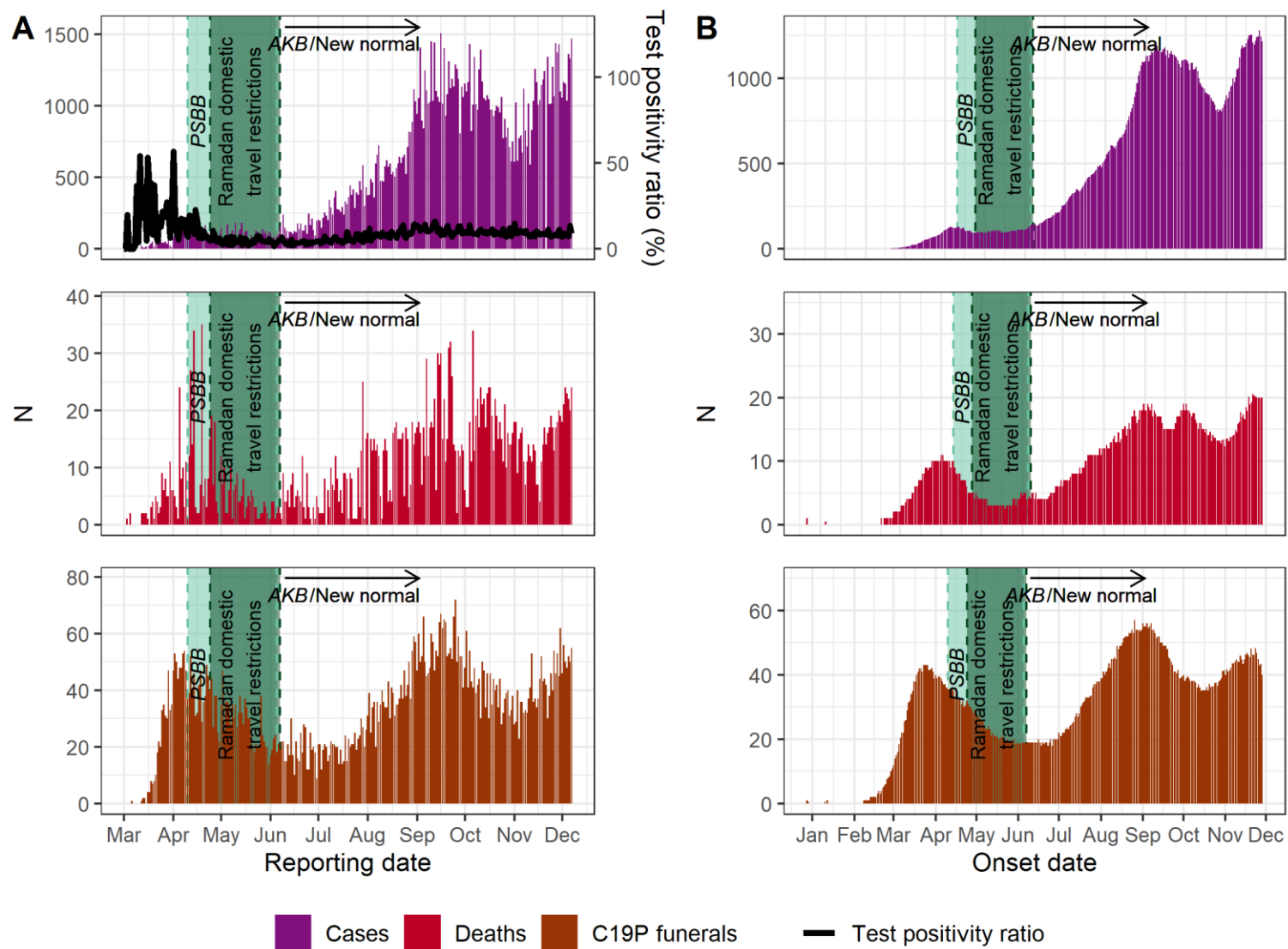


Figure 2.2. Temporal trends of the three surveillance metrics and their stochastic reconstructions. **A)** Barplots of temporal trends of metrics captured by the Jakarta routine surveillance data for COVID-19. Each row represents a metric from the surveillance data. They are (from top to bottom) the daily number of reported confirmed COVID-19 cases with test positivity ratio (the proportion of tests that are positives), the daily number of reported deaths of confirmed COVID-19 cases, and the daily number of funerals with COVID-19 protocols (C19P). **B)** Barplots representing the median daily frequency of symptom onsets based on 100 stochastic reconstructions. Each row represents the estimated daily frequencies of onset based on (from top to bottom) confirmed COVID-19 cases, confirmed COVID-19 deaths, and C19P funerals. The tail ends (last nine days) of the reconstructed onset frequencies were removed from the graphs due to the high uncertainty of the estimates. The light-green shaded areas in both A and B graphs denote the period of PSBB, while the dark-green area denotes the additional Ramadan domestic travel restrictions.

The temporal trends of the transformed confirmed COVID-19 cases showed two epidemic peaks, each during the first PSBB in mid-April 2020 and the second PSBB in mid-September 2020 (**Figure 2.2B**, top row). Data on C19P funerals (**Figure 2.2B**, bottom row) suggest that the first peak in infections likely occurred earlier in mid-March. Based on the confirmed deaths data, the estimated timing of the first infection peak (**Figure 2.2B**, middle row) lies between the confirmed cases peaks and C19P funeral peaks. For the second peak, however, all transformed data showed similar timings just before the second PSBB started. In contrast to the transformed case data, which produces a second peak much higher than the first, transformed C19P funeral trends suggested that the first and second peaks were likely of comparable magnitude. Based on the transformed deaths data, the second infection peak is also higher than the initial one, although the relative difference is not as extreme as the cases-based infection peaks.

Figure 2.3 show the daily changes in the non-residential population mobility in Jakarta. This suggests population mobility dropped significantly in early March, far before the implementation of PSBB in early April. Population mobility remained low throughout PSBB and started to recover in June after Jakarta entered the ‘new normal’ period. Another decline in population mobility was also observed during the second PSBB. However, the decline was lower than observed in the first PSBB in April. Jakarta's overall non-residential population mobility remained lower than the baseline values throughout 2020.

To further understand the population transmission dynamics of SARS-CoV-2 in Jakarta, R_t values were calculated and shown in **Figure 2.3**. The estimated R_t values shown in **Figure 2.3** support the substantial impact of NPIs implementation when applied to all three surveillance metrics. The estimated R_t during the initial phase of the epidemic is estimated to be around 1.5 to 2.5. R_t subsequently declined to below 1 during the first PSBB period, followed by an increase to slightly above 1 as Jakarta entered the ‘new normal’ period (or AKB) in early June. The reimposition of PSBB in September 2020 also brought the R_t below 1. The R_t estimates based on C19P funerals (**Figure 2.3C**) data show an earlier decline to below 1 than estimates based on confirmed cases (**Figure 2.3A**) and deaths (**Figure 2.3B**), which happened soon after the average non-residential mobility was reduced by more than 40% before the first PSBB. Furthermore, R_t estimates based on C19P funerals also suggest a more sustained impact of the implementation of PSBB with no median estimates of R_t above 1 during PSBB.

Finally, **Figure 2.4A** shows a strong and significant correlation between R_t estimates with the observed mobility patterns as measured by the Google Community Mobility Reports (0.91, 0.72, and 0.92 for confirmed cases, confirmed deaths, and C19P funerals, respectively, all with p-value

< 0.001) observed before the lifting of the first PSBB. However, little correlation (or no correlations based on confirmed cases and confirmed deaths) was observed after the lifting of the first PSBB or the AKB period (**Figure 2.4B**). This result suggests a decoupling between transmission and mobility, whereby estimates of R_t during periods of equivalent levels of mobility during AKB are lower than estimates obtained before AKB.

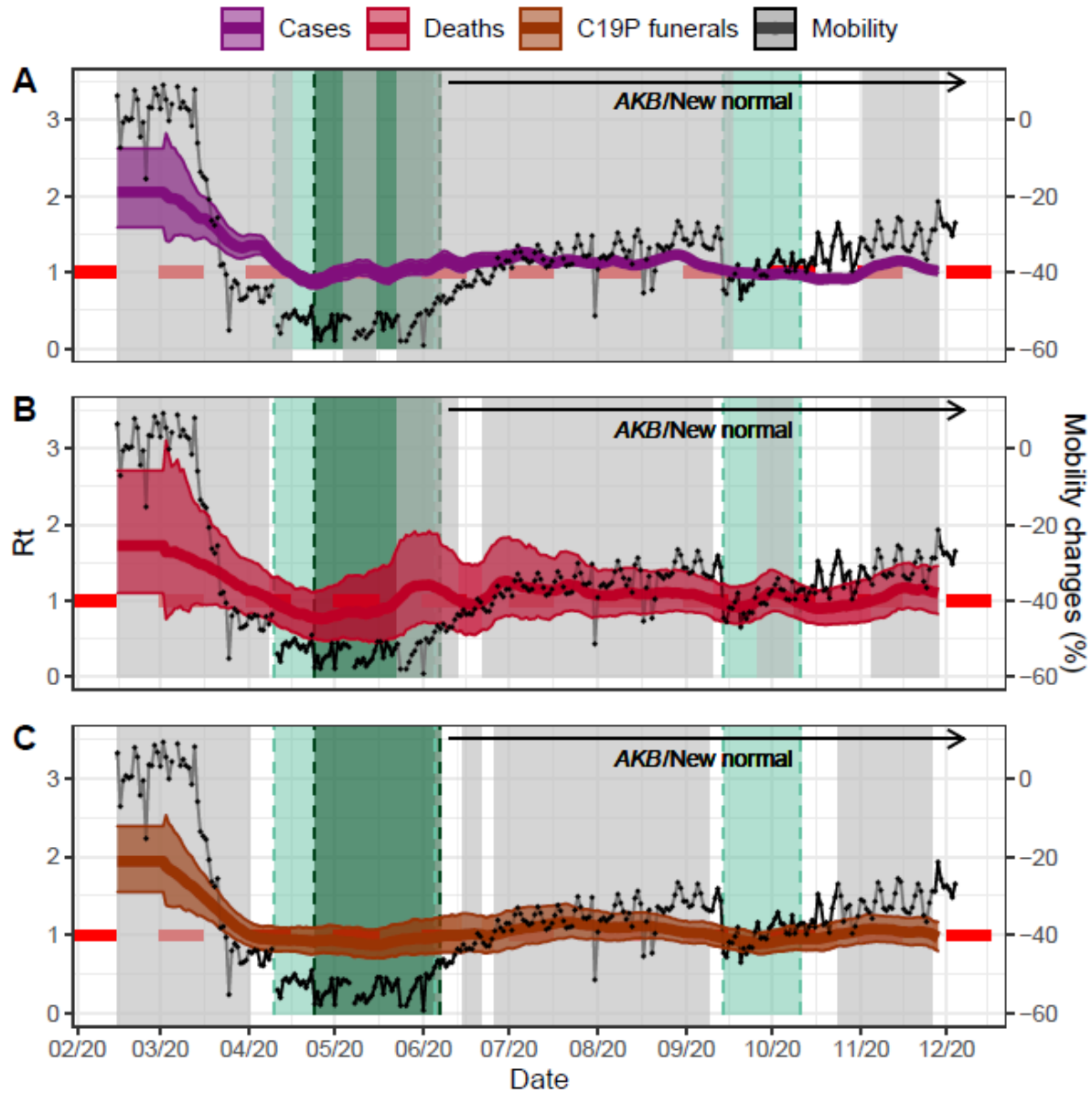


Figure 2.3. Line plots representing the median estimates of R_t with their respective 95% credible intervals (left y-axis). A) R_t estimates based on confirmed COVID-19 cases; B) R_t estimates based on confirmed COVID-19 deaths; and C) R_t estimates based on C19P funerals. Black lines and dots denote average changes in non-residential mobility (right y-axis). The light-green shaded area denotes the period of PSBB, while the dark-green area denotes the additional Ramadan domestic travel restrictions. Grey-shaded areas denote periods where the estimated medians of R_t are above 1.

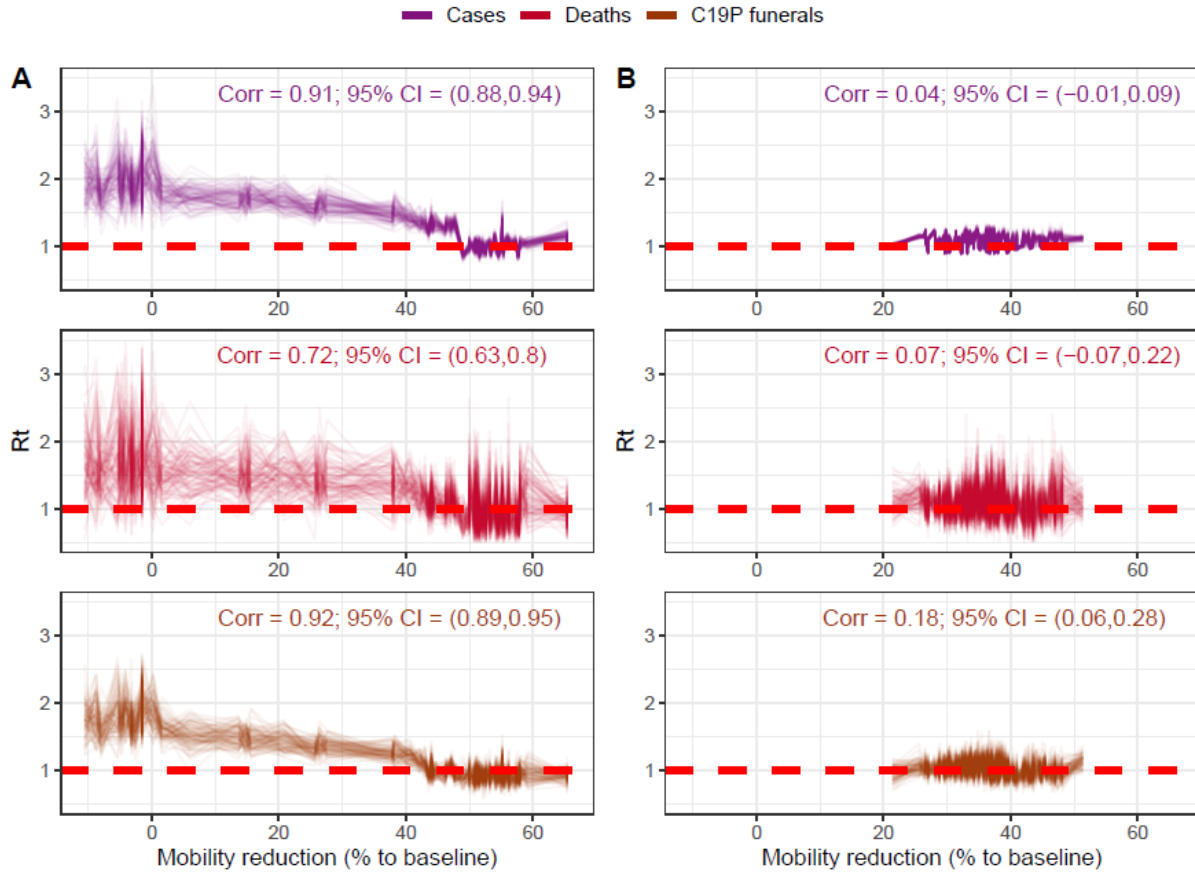


Figure 2.4. Line plots representing the relationship between the estimated R_t and the average non-residential mobility reduction for R_t estimates based on confirmed COVID-19 cases, confirmed COVID-19 deaths, and C19P funerals. Pearson's correlation coefficients between the two metrics are shown. A) Correlations before the 'new normal' period (or AKB); and B) Correlations after the 'new normal' period (or AKB).

2.4 Discussions

The analysis presented in this chapter shows the considerable benefits of using syndromic measures of COVID-19 mortality, such as the C19P funerals data, to better measure the past burden and the ongoing dynamics of an epidemic. These results support the 'hypothesis' of substantial circulation of SARS-CoV-2 in Indonesia well before the first confirmed COVID-19 case (Salazar et al., 2020). This 'hypothesis' is also further corroborated by Elyazar et al.'s findings, which highlighted a significant increase in burials as early as January 2020 in Jakarta (I. R. Elyazar et al., 2020). Simultaneously, they also indicate an earlier decline in transmission during the early stages of the pandemic, coinciding with reductions in mobility. My estimates also showed more sustained declines in transmissibility in response to NPIs than observed in confirmed

COVID-19 deaths data alone which may reflect reality given limitations in achieving antemortem diagnosis during the peak of the first wave.

That R_t estimates based on C19P funeral data have higher correlations with the changes in non-residential mobility than estimates based on reported cases and deaths also supports the added value of the data. This is partly because data reconstructions using onset-to-diagnosis and onset-to-death delays could not account for the ‘event-to-reporting’ delay. C19P funerals data, on the other hand, represent the actual number of funerals on the day, producing less biased reconstructed onset dates. Moreover, reported case and death data were often subject to periods of inconsistent testing and reporting, which caused spikes in the data, and, therefore, caused R_t estimates from those data to sometimes fall above 1 during periods of PSBB. Finally, like in other countries, the decoupling of the virus transmissibility and the observed human mobility measures after the reopening of the restrictions period was also found in this analysis (Fiori et al., 2022; Nouvellet et al., 2021).

However, whilst these data, and other similar measures of suspected mortality, provide a valuable alternative lens to understanding the COVID-19 burden and dynamics, they still do not allow precise measurement. Without confirmed diagnoses, the proportion of infected individuals will always be unknown and liable to vary spatiotemporally. This also applies to the extent to which measures of suspected deaths represent all deaths of individuals displaying COVID-19 symptoms. Complementing the burden estimates from syndromic measures of mortality with seroprevalence survey data, for example, would give better confidence on how much the data reflects population burdens. Additionally, there are relatively long delays between the onset of symptoms and death. The data reconstruction method used in this study causes a loss of information, especially for the period of approximately a week before the reporting date, due to high uncertainty in the reconstructed data. Recently, nowcasting methods that would account better for these uncertainties have been developed, creating opportunities for implementing the methods to these data in the future (Hawryluk et al., 2021). Nevertheless, collecting such data is likely to yield high value for many countries where testing capacity has been severely strained in the face of the pandemic and for future pandemics of respiratory pathogens that require developing new diagnostic capacity.

2.5 Conclusions

During the early phase of the pandemic, many countries, especially the lower and middle-income ones, struggled to keep track of the currently emerging epidemics in their countries as they lacked

the capacity for testing. This study shows the benefit of collecting syndromic measures of mortality, such as C19P funerals data collected in Jakarta, Indonesia, to give a better perspective on how the pandemic unfolds in the population. These data could give us a better view of the relative levels of infections in the populations and detect the changes in transmission trajectories earlier, allowing the government and the community to react to the situation more rapidly and with a greater degree of confidence than when relying only upon reported cases and deaths data.

Chapter 3: Modelling district-level COVID-19 spread in Java and the impact of Ramadan travel restrictions using a mechanistic metapopulation model

Movement restrictions formed a core part of the early response to the COVID-19 pandemic in many countries across the globe. Similarly, in Indonesia, Pembatasan Sosial Berskala Besar (PSBB, Large Scale Social Restrictions in English) implemented by the government during that period also involved some scales of movement restrictions, including inter-district movement restrictions. One of the largest inter-district movements in Indonesia happens during and especially at the end of the Ramadan month. During this time, Muslims in Indonesia usually do the 'mudik' tradition, visiting their families in their hometowns to celebrate Eid al Fitr together at the end of Ramadan. During the first PSBB period of 2020, the government banned inter-district travel during and shortly after Ramadan. The restriction was implemented to prevent the spread of COVID-19 from the epicentres of the epidemic in large cities, especially on Java Island, to the 'mudik' destinations, which are usually the more rural areas across the country. In this chapter, I developed a metapopulation model to investigate various scenarios involving the potential impact of this movement restrictions policy on the severity and burden of COVID-19 at the district level in Java, accounting for differences in healthcare capacity and population age structures.

3.1 Introductions

3.1.1 Background

Jakarta represented the initial epicentre of the COVID-19 pandemic in Indonesia in early 2020 (Rochmyaningsih, 2020). However, by 9th April 2020, COVID-19 cases had been reported in all provinces in Indonesia (Andriyanto, 2020). On 10th April 2020, a large-scale movement restriction named PSBB was implemented to reduce the transmission and spread of COVID-19 in the country (WHO Indonesia, 2020). Amongst restrictions included during the first PSBB in Indonesia were the inter-district travel restrictions during the Ramadan festive month across the country.

In Java, the Ramadan period, as with major holidays in other countries, such as Christmas, and Chinese New Year, is associated with changes in human mobility patterns (Hu, 2019; Lai et al., 2022). During the holiday period, increases in mobility from urban to rural areas are observed, while after the holidays, movements back to the urban areas increase (Lai et al., 2022). For

example, in Indonesia, the Ramadan month exodus, usually called 'mudik', has traditionally been the largest seasonal human migration in the country (Prasetyo & Warsono, 2017). In 2019, it was estimated that more than 33 million people performed 'mudik' during Ramadan and Eid-al-Fitr festivity (Herman, 2019). The 'mudik' tradition, similar to the major holiday movements in other countries, involves large-scale movements of people from urban to rural areas. Three cities in Java are the main origins or sources of human movements during the Ramadan period; they are Jakarta, Bandung (West Java), and Surabaya (East Java) (Prasetyo & Warsono, 2017).

In the context of COVID-19 in Indonesia, preventing the spread of the disease to the rural populations was considered important, at least due to two characteristics of the rural population in Indonesia: the population age structure and the access to healthcare facilities. In Indonesia, rural areas are generally older than urban areas (G. W. Jones, 2016; Utomo et al., 2019). As COVID-19 severity disproportionately affects people in old age (Verity et al., 2020), COVID-19 spread in rural areas of Indonesia could cause more severe burdens on the population. Meanwhile, people who live in rural areas in Indonesia have less access to and utilisation of healthcare facilities (Sujarwoto & Maharani, 2022; Wulandari et al., 2022), where some factors affect their access to healthcare facilities, such as distance, distribution, and capacities (Wenang et al., 2021).

In this study, I focused on the potential spread of COVID-19 during the first wave of the epidemic in Indonesia to the older rural populations with low access to healthcare facilities on Java Island. A type of mathematical model that can help understand the spread of disease in a network of districts is the metapopulation model, as it considers interactions between different subpopulations (in this case, districts) and the movements of individuals between them (Grenfell & Harwood, 1997). Therefore, I developed a metapopulation model of COVID-19 at the district level to simulate the spread of the disease in Java Island, accounting for within- and between-district population mobility. Several COVID-19 transmission and population mobility scenarios were simulated and then validated using publicly available data to evaluate the impact of the movement restrictions, especially during Ramadan in Java Island.

3.1.2 Aims

In this chapter, the analysis focused on the spatial spread of COVID-19 across districts in Java Island. I aimed to:

1. Develop a metapopulation model representing a district-level spatial spread of COVID-19 in Java Island.

2. Estimate the potential impact of COVID-19 spread to districts in Java Island, where risk factors in demography and healthcare access were heterogeneous.
3. Provide insight into the likely effectiveness of inter-district movement restrictions implemented, especially during the Ramadan month of 2020.

3.2 Data and methods

3.2.1 Data

3.2.1.1 Epidemiological data

Daily reported COVID-19 cases and reported deaths in Jakarta province were obtained from the official Jakarta COVID-19 monitoring website: <https://corona.jakarta.go.id/id/data-pemantauan> (Jakarta Provincial Health Department, 2020). Daily reported cases and reported deaths for five other provinces in Java (Banten, West Java, Central Java, Yogyakarta, and East Java) were obtained from an independently curated online spreadsheet by a crowdsourcing organisation KawalCOVID19 (kcov.id/daftarpositif) based on the daily publication by the Indonesia COVID-19 National Task Force (Indonesia COVID-19 Task Force, 2020; KawalCOVID19, 2020). The data were collated up to 7th December 2020. In addition, the weekly numbers of deaths of suspected and probable COVID-19 cases were obtained from WHO Indonesia situation reports 13-36 (WHO Indonesia, 2020).

A suspected case refers to a person or patient who meets the clinical criteria of COVID-19 (fever, cough, fatigue, headache, myalgia, sore throat, to name a few) or is epidemiologically linked through contact with a probable case, confirmed case or a cluster of COVID-19 cases. A probable case is a suspected case with an acute upper respiratory infection (URI) or acute respiratory distress syndrome (ARDS), or someone who has died with convincing clinical symptoms of COVID-19 but has not yet received their confirmatory test result (Ministry of Health of the Republic of Indonesia, 2020d). Both suspected and probable COVID-19 cases have yet to be tested or receive the results of their COVID-19 laboratory confirmations. Thus, they were not included in the reported COVID-19 cases and deaths if they died (only the laboratory-confirmed cases were included).

3.2.1.2 Population data and rural-urban district classifications

Population data in terms of total population and population by age group for all districts in Java Island were obtained from the 2020 Census results (Badan Pusat Statistik, 2021). Province-level population counts are shown in **Table 3.1**. I used these steps in this thesis to classify districts into

urban or rural. First, using Statistics Indonesia (Badan Pusat Statistik/BPS) urban-rural village (the smallest administrative unit in Indonesia) classifications, villages in Java Island were classified as either rural or urban (Putri et al., 2022; Statistics Indonesia, 2019). Then, districts in Java were classified into either urban or rural districts based on the proportion of rural villages in their territories. When the proportion of rural villages is larger than urban, the district is classified as rural and vice versa.

Table 3.1 Province-level population counts in 2020 for provinces in Java Island.

Province	Population
Jakarta	10,576,400
West Java	49,565,200
Central Java	34,738,200
Yogyakarta	3,919,200
East Java	39,955,900
Banten	12,895,300

3.2.1.3 Call detail records (CDRs) data

Anonymised call detail records (CDRs) data from one of the biggest telecommunication companies in Indonesia from 1st May 2011 to 30th April 2012 were used to estimate between-district movement matrices for the Ramadan and non-Ramadan periods. The CDRs data were collected daily with a total of 266 billion records and 137 million unique SIM cards. Each record of the CDRs represents a call activity (voice, short messaging service) and the ID of the mobile phone tower closest to the location of the person making the call—a total of 17,319 mobile phone towers operated during the period of CDRs data collection across the country. The mobile tower locations were then mapped to districts.

3.2.1.4 Province-level changes in population mobility

Similar to **Chapter 2**, the province-level changes in population mobility data were obtained from Google COVID-19 Community Mobility Reports (Google LLC, 2020). Changes in the population mobility for provinces in Java Island (Jakarta, Banten, West Java, Central Java, Yogyakarta, and East Java) up to 7th December 2020 were used for the analysis.

3.2.1.5 Healthcare capacity data

District-level hospital and intensive-care unit (ICU) bed data were obtained from the Online Healthcare Facilities (Fasyankes Online) website by the Directorate of General Health Services (Ditjen Yankes) of the Ministry of Health of the Republic of Indonesia (Directorate General of Health Services Ministry of Health of the Republic of Indonesia, 2020).

3.2.2 Methods

3.2.2.1 Estimating movement matrices from aggregated CDRs data

District level (city and municipality, 115 in total) movement matrices (M) prior to the pandemic for the normal (or non-Ramadan) (M_N) and Ramadan (M_R) periods were calculated from CDRs data. Each element of the matrix ($m_{i,j}$) represents the proportion of days spent by residents of District i in District j over the year.

The daily position of each user is described as the district with the most frequent mobile phone activities within a single day. All users were assumed to be active from the first to the last day of their phone usage. On days where no activities were recorded during the active period, the user's position was assumed to be the same as the previous day. The primary residence of each user is defined as the district where the users spend most of their days over their 'active' period (Wesolowski et al., 2012). For example, if user X had active days of 100 days, then spent 75 days in District Y and 25 days in District Z, the primary residence of user X is District Y.

Based on their daily locations and primary residences, the proportions of days spent by people from District i , their primary residences, in District j , where they spent their day, were then calculated. First, M_R was estimated using data from August to September 2011 (the period of the Ramadan month, Eid celebration, and national holidays). Then, M_N was estimated using the rest of the data that were not used to estimate M_R (May 2011 - July 2011 and October 2011 - April 2012 periods).

All districts in Java Island were represented as a single row in each matrix, with exceptions for districts in Jakarta province, which were represented as an aggregated single row ($i = 1$). This was done due to the nature of Jakarta province as a 'megacity' in Java, where the population is largely urbanised, and its size and population are much smaller than other provinces in Java. Modelling Jakarta as a single subpopulation may better reflect the high degree of connectivity between the urban districts within the province while adding simplicity to the model. Outside-Java movements were also represented as a single row ($i = 2$). **Table S3.1** shows a complete list of

districts (including Jakarta and outside Java) and each respective index in the movement matrices.

3.2.2.2 Extrapolating Java Island district-level daily COVID-19 transmissibility (R_t) based on the relationship between R_t and population mobility in Jakarta

Province-level daily effective reproduction number (R_t) was estimated using the relationship between R_t estimates based on funerals with COVID-19 protocol (C19P) data in Jakarta ($R_{t,funerals}$) and population mobility, using only data before the lifting of the first PSBB. For the population mobility metric, I used the 7-day rolling averages of changes in non-residential mobility. Then, those changes in mobility were fitted to 100 posterior samples of the estimated $R_{t,funerals}$ (estimated in **Chapter 2**), using smoothing spline models. The smoothing spline model was implemented in R software using `smooth.spline` function with four knots. The models were then used to extrapolate the daily values of R_t for other provinces in Java Island based on their 7-day rolling averages of changes in non-residential mobility based on the province-level Google Community Mobility Reports (Google LLC, 2020).

These province-level extrapolations of R_t were then used as district-level R_t in provinces other than Jakarta. However, to account for potential differences in contact patterns in urban and rural districts in Java Island, further adjustments for district-level transmissibility were needed. A more detailed explanation of these adjustments based on transmission simulation scenarios will be provided in section 3.2.2.4.

3.2.2.3 Metapopulation model structure of COVID-19 spread in Java

A metapopulation model was developed to simulate the district-level spread of COVID-19 in Java Island. Each patch in the metapopulation model represents districts ($i = 1, 2, \dots, 115$) listed in **Table S3.1**. For each patch, stochastic differential equations representing a Susceptible-Exposed-Infected-Recovered (SEIR) model were implemented (overall structures in **Figure 3.1A**). The equations are as follows:

$$\begin{aligned}\frac{dS_i}{dt} &= -new\ infections_i \\ \frac{dE_i}{dt} &= new\ infections_i - \alpha E_i \\ \frac{dI_{mild,i}}{dt} &= (1 - p_{hosp,i})\alpha E_i - \gamma_1 I_{mild,i}\end{aligned}$$

$$\frac{dI_{case,i}}{dt} = p_{hosp,i}\alpha E_i - \gamma_2 I_{case,i}$$

$$\frac{dR_i}{dt} = \gamma_1 I_{mild,i} + \gamma_2 I_{case,i}$$

where *new infections_i* is the number of new infections in each patch based on the stochastic adaption of the metapopulation model by Keeling et al. (Keeling et al., 2010), α is the per-capita transition rate reflecting the mean duration of the latent period, p_{hosp} is the probability of having severe illness and needing hospitalisations, $p_{critical|hosp}$ is the probability of needing critical care if hospitalised, and γ_1 and γ_2 are the per-capita transition rate reflecting the mean duration of infectiousness of mild and severe infections, respectively. The severity and duration parameters of the model were derived from other analyses. The full model parameter descriptions, specifications, and sources of their values are available in **Table S3.2**.

To calculate *new infections_i*, we first need to calculate the district-level force of infections, λ_i , that accounts for inter-district movements of both susceptible individuals (that might acquire infections in other districts) and infected individuals (that might infect people in other districts) based on the inter-patch connectivity (the movement matrix, M , accounting daily changes in mobility - see section 3.2.2.1). Then, the total number of infected individuals that are contributing to infections in district i , $I_{tot,i}$, is calculated by:

$$I_{tot,i} = \sum_{j=1}^{115} Binomial(I_j, m_{j,i})$$

The basic reproduction number at district i ($R_{0,i}$) of this metapopulation model is defined as:

$$R_{0,i} = \beta_i((1 - p_{hosp,i})\gamma_1 + p_{hosp,i}\gamma_2)$$

where β_i is the transmission rate of each district. Based on the $R_{0,i}$ equation, β_i is calculated by:

$$\beta_i = \frac{R_{0,i}}{((1 - p_{hosp,i})\gamma_1 + p_{hosp,i}\gamma_2)}$$

$R_{0,i}$ is represented by the value of R_t estimated for the period of maximum mobility recorded within the Google Community Mobility Reports data. Then, the district-level force of infections (λ_i) can be calculated using the following equation:

$$\lambda_i = \beta_i \times \kappa_{t,i} \times \frac{I_{tot,i}}{N_i},$$

where N_i is the total population of each district/patch, and $\kappa_{t,i}$ is the daily ratio between the estimated $R_{t,i}$ values based on the spline model estimates and the respective $R_{0,i}$, representing the relative changes in the daily transmission rate. I did not model transmission outside Java and assumed no importation of cases from outside Java as this analysis focused on the impact of the COVID-19 spread in Java, primarily from the initial epicentre in Jakarta. However, I still allowed movements to and from that patch ($i = 2$), which implies that both I_2 and λ_2 are always 0. $new\ infections_i$ are then calculated as follows:

$$new\ infections_i = \sum_{j=1}^{115} Binomial(S_i \times m_{i,j}, (1 - \exp(-\lambda_j)))$$

For each severe infection needing hospitalisation (I_{case}), the case was either deemed a critical case (i.e., indicated to require an ICU bed) with probability $p_{critical|hosp}$ and otherwise, non-critical (i.e., indicated to require an isolation bed) with an associated probability of death of $p_{death|critical}$ and $p_{death|non-critical}$, respectively (diagram in **Figure 3.1B**). p_{hosp} , $p_{critical|hosp}$, $p_{death|critical}$, and $p_{death|non-critical}$ were obtained for each district as the average values estimated within simulations from the `squire` R package (MRC Centre for Global Infectious Disease Analysis, 2020; Watson et al., 2020). The estimates consider the age structure of the demography of each district based on the 2020 census data (Badan Pusat Statistik, 2021). In the absence of equivalent data from Java, between age groups mixing patterns based upon a contact survey from Shanghai province, China, were used as an input for the `squire` model as an example of contact patterns within a megacity of a middle-income Asian country.

3.2.2.4 Metapopulation model simulation frameworks of COVID-19 spread in Java

The metapopulation model was simulated with 100 replicates by seeding initial cases in Jakarta and Kota Surabaya (East Java's capital) - both have international airports receiving travellers from China - on 7th January 2020 (arbitrarily selected). The number of seeded cases in Jakarta was calibrated by eye to provide simulated death trends bounded by the interval between reported COVID-19 deaths and C19P funerals, producing an initial number of 12. Initial cases in Surabaya were drawn according to a binomial draw assuming an underlying importation rate of 60% of that in Jakarta (based on the relative volume of incoming travellers). Random numbers based on the Binomial distribution were sampled for each replicate.

Different transmission scenarios were assumed for rural and urban districts. The classification of a district's urban/rural status was based on the urban/rural classification of most villages within

the district. $R_{t,i}$ values for all districts were assigned to be the province-level value of $R_{t,i}$ in which each district is located. I then explore the possibilities for rural districts to have different $R_{t,i}$ levels compared to urban districts (possibly lower), ranging from 100% to 60% of the province-level $R_{t,i}$. In the results section, simulation results assuming rural districts $R_{t,i}$ to be 90% of $R_{t,i}$ in urban districts were shown. The full list of the urban-rural transmission scenarios is shown in **Table 3.2**.

During Ramadan and Eid festivals, from 24th April 2020 up to 7th June 2020, the Ramadan movement matrix (M_R) was used as the baseline movement matrix. In the other period, the non-Ramadan movement matrix (M_N) was used as the baseline movement matrix. As a baseline scenario, throughout the simulation, the proportions of people spending their time in the other districts ($m_{i,j}$ where $i \neq j$) were adjusted by the province-level changes in mobility over time. However, I assumed the reductions in large-scale movements outside the province were higher than those within the province (changes in mobility according to Google Data) according to an odds ratio (OR) of 2 within the default scenario. A sensitivity analysis assuming a larger value of OR was done and presented in the supplementary figures.

For each simulation scenario (**Table 3.3**), I also devised a metric to assess the extent to which the epidemic would likely strain available healthcare resources over time, given patterns of spatial spread and disparities in healthcare supply at the district level. This metric was defined by determining the number of available beds for each individual newly requiring hospitalisation each day within the model by subtracting the number of hospital beds required in the simulation from the total hospital beds capacity available at the district level obtained from the Online Healthcare Facilities website (Directorate General of Health Services Ministry of Health of the Republic of Indonesia, 2020).

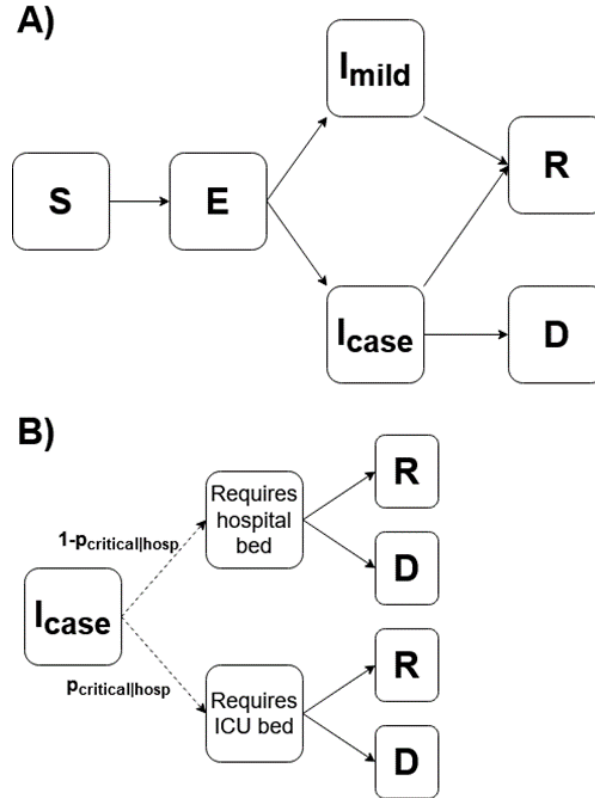


Figure 3.1. SEIR model structure. A) The SEIR model structure for each patch in the metapopulation model. Susceptible individuals (S), if infected, progress to the exposed compartment (E), having their latent period of infections. Then, those individuals will either develop mild symptoms (I_{mild}) or severe symptoms requiring hospitalisations (I_{case}). Those who develop severe symptoms may have two possible outcomes: recovery (R) or death (D). B) The pathway of infections requiring hospitalisations (I_{case}). Each infection with severe symptoms may only need a standard hospital bed or develop worse conditions that require critical care (ICU bed). Each case treated in critical and non-critical care may recover or die based on specific probabilities. Dashed lines denote probabilistic pathways, not rates of transition.

Table 3.2. List of transmission scenarios for the rural districts R_t adjustments.

Scenario name	Details
Rural 100%	R_0 and R_t of urban and rural districts in each province were assumed to be the same.
Rural 90%	R_0 and R_t of rural districts in each province were assumed to be 90% of the province-level R_0 and R_t . Used as the main transmission scenario shown in the main text's results.
Rural 75%	R_0 and R_t of rural districts in each province were assumed to be 75% of the province-level R_0 and R_t .
Rural 60%	R_0 and R_t of rural districts in each province were assumed to be 60% of the province-level R_0 and R_t .

Table 3.3. Metapopulation model simulation scenarios (one baseline scenario and four counterfactual scenarios).

Scenario name	Details	Transmission scenario used
Baseline	Movement from a district is assumed to reduce according to reductions in movement within a district scaled by an odds ratio of 2 to reflect an assumed lower likelihood of long-distance travel.	Rural 90%
Ramadan 1	No movement reductions between districts during the Ramadan and Eid festivals period and the R_t values during the period were assumed to be similar to the baseline scenario.	Rural 90%
Ramadan 2	No movement reductions between districts during the Ramadan and Eid festivals period and the R_t values during the period were assumed to be 75% of each district $R_{0,i}$.	Rural 90%
Ramadan 3	No movement reductions between districts during the Ramadan and Eid festivals period and the R_t values during the period were assumed to be the same as each district $R_{0,i}$.	Rural 90%
Unmitigated	No interventions assumed which implies no movement reductions over all period of simulations with the R_t values to be the same as each district $R_{0,i}$ over the period of simulations.	Rural 90%

3.3 Results

Substantial variations exist across the island regarding demography, healthcare capacity, and between-district mobility. These factors may contribute to the severity and burden of COVID-19 in each district, the capacity that healthcare facilities can absorb, and how quickly COVID-19 can be spread into and within those districts. **Figure 3.2A** shows the district-level proportions of the population over the age of 50 in Java Island. The proportion of individuals over 50 was typically higher (26%) in rural districts than in urban ones (19%). There were also substantial disparities in healthcare availability at the district level, ranging from the comparatively well-resourced Jakarta setting (2.22 hospital beds per thousand population) to the poorer, more rural setting of Tasikmalaya in West Java (0.18 beds per thousand population) (**Figure 3.2B**). Patterns of between-district mobility outside of the window of the pandemic estimated using mobile phone

data throughout 1st May 2011 - 30th April 2012 highlight the extent to which these settings were connected. **Figures 3.2C** and **3.2D** highlight changes in the mobility patterns that originated from Jakarta to other districts on the island, comparing population mobility occurring during Ramadan and outside Ramadan. These suggest how between-district connectivity was particularly high during the Ramadan period, with increased large-scale movements from densely populated Jakarta to other more rural regions with lower availability of healthcare. While during the non-Ramadan period, mobility from Jakarta largely happened across its surrounding satellite cities and districts.

Figure 3.3 shows the timeline of COVID-19 interventions, the burden of COVID-19 over time, and their geographical distributions in Java Island (data up to 7th December 2020). Reported COVID-19 cases in Java Island were generally higher in Jakarta than in other provinces on the island. However, East Java led the reported COVID-19 deaths until the end of 2020. These show how the differences in COVID-19 testing might affect the patterns we see in reported COVID-19 cases and deaths. Jakarta, the province with the highest testing capacity per capita in the country, was able to capture more COVID-19 cases in the community. Lower case-to-death ratios in other provinces may indicate that COVID-19 testing was prioritised for those with acute conditions in healthcare facilities. Furthermore, in other provinces in Java except for Jakarta, increasing patterns in reported COVID-19 cases and deaths also occurred throughout the first PSBB, which may be a function of both the increased seeding of COVID-19 cases in the rural populations in Java during that period, as well as improved testing capacities over time.

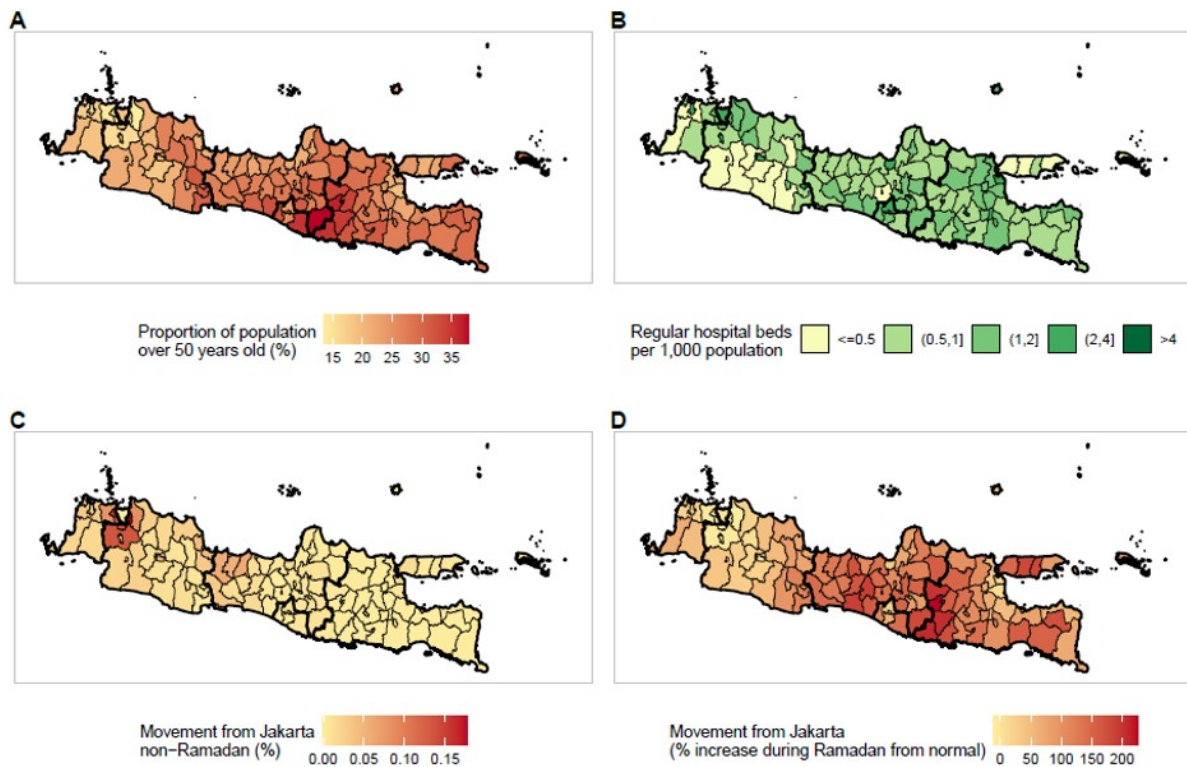


Figure 3.2. Key factors affecting the spread and severity of the COVID-19 epidemic in Java, Indonesia. A) Proportion of the population aged over 50 years old at the district level. B) Number of regular hospital beds per one thousand population at the district level. C) Proportion of Jakarta residents who spent their day in other districts in Java during a non-Ramadan period. D) Increased proportion of people of Jakarta who spent their day in other districts in Java during Ramadan compared to the non-Ramadan period.

Figure 3.4A shows the modelled relationship between mobility and R_t obtained from the Jakarta C19P funeral data using smoothing splines before the lifting of the first PSBB (see **Chapter 2**). Those modelled relationships were then applied to trends in mobility data from the remaining provinces in Java (**Figure 3.4B**). The modelled R_t suggests large reductions in transmission in all provinces coinciding with the first PSBB period. However, they also suggest that measures were sufficient to bring R_t below 1 for a sustained period only in Jakarta and Yogyakarta. Increases in mobility occurred either during early May (Banten, West Java, Central Java, and East Java) or alongside the establishment of the AKB in June (Jakarta and Yogyakarta), leading to corresponding increases in our estimates of R_t (**Figure 3.4B**). These estimates supported the early increases in reported COVID-19 cases and deaths in provinces other than Jakarta throughout the PSBB period (**Figure 3.3A** and **3.3B**).

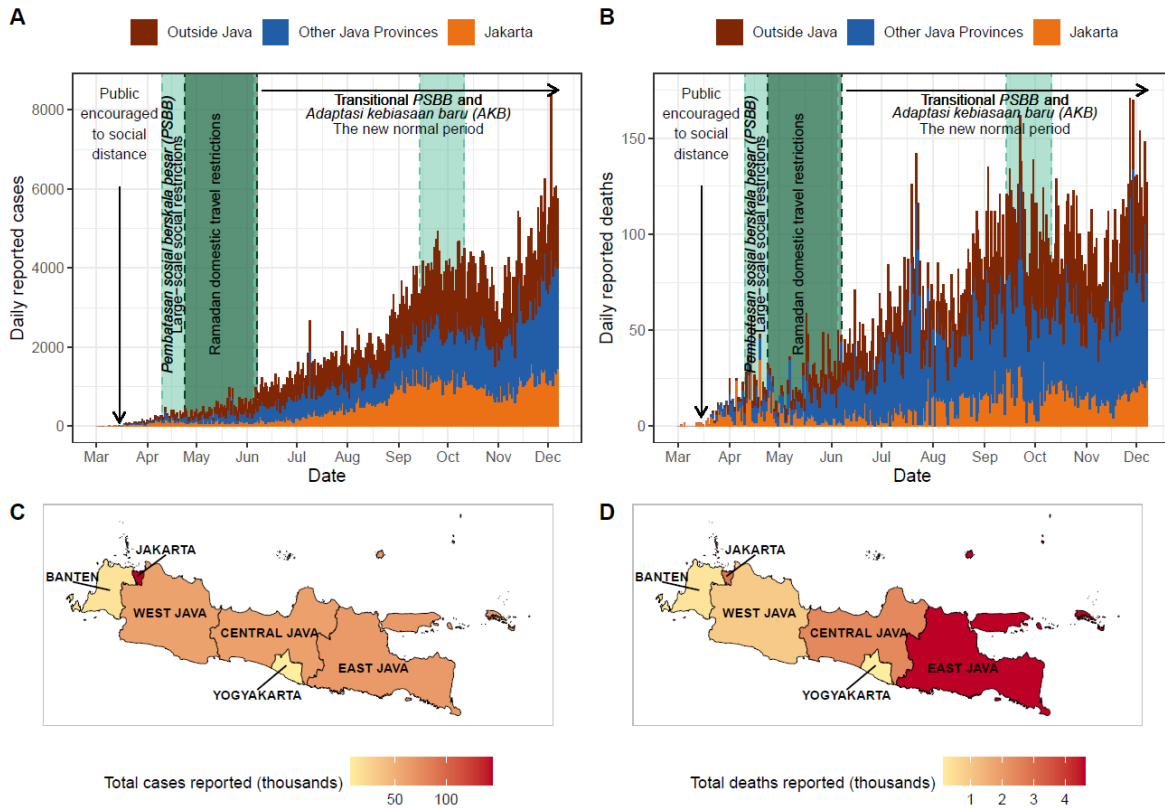


Figure 3.3. The burden of COVID-19 and timeline of interventions in Indonesia (data up to 7th December 2020). A) The daily number of reported COVID-19 cases. B) The daily number of reported COVID-19 deaths. C) Total reported COVID-19 cases at the province level on Java Island. D) Total reported COVID-19 deaths at the province level on Java Island.

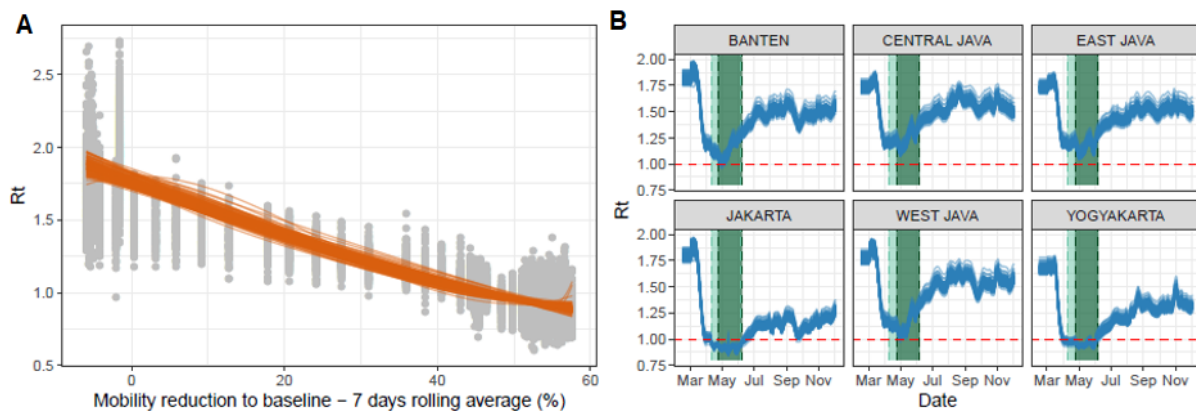


Figure 3.4. A) The relationship between the estimated R_t values based on C19P funerals data and the average reduction in non-residential mobility in Jakarta using data only before the lifting of the first PSBB. Grey dots represent 100 samples of R_t values. Orange lines show the modelled smoothing spline relationship between 100 samples of R_t values and mobility reduction. B) Extrapolations of R_t values in Java provinces based on Google Mobility trends for each province and the 100 sampled smoothing splines in Figure 3.4A (orange lines). Light green shaded areas denote periods of PSBB, while the dark green shaded areas represent the period of Ramadan domestic travel restrictions.

These R_t estimates were then integrated into the metapopulation model. **Figure 3.5A** shows the estimated daily COVID-19 reported deaths based on the metapopulation model under the baseline and unmitigated scenarios, summarised at the province level, and compared those estimates to the daily confirmed and suspected COVID-19 deaths. Estimates of deaths in the baseline scenario were consistent with observed qualitative patterns prior to the shift to the AKB phase of the epidemic in early June. The epicentre shifted over time from Jakarta to satellite towns and other provincial capitals, with Yogyakarta remaining the least affected. Furthermore, the baseline scenario's median deaths fall within the range of cumulative confirmed and suspected deaths up to 31st May 2020 and the number of confirmed and suspected deaths between 13th-31st May 2020 in most provinces (**Table 3.4**). Finally, total suspected deaths fell within the model's uncertainty bounds for most provinces except Jakarta and Central Java. The analysis shows how the metapopulation model could simulate reasonable COVID-19 spread scenarios at the province level in Java Island before and during the first PSBB.

Furthermore, the scenario estimates are consistent with reductions in contact rates serving to reduce spread, reduce healthcare demand and avert mortality prior to the AKB phase. The model estimated 57,000 (24,800-105,400, 95% Uncertainty Interval/UI) deaths averted when compared to an effectively unmitigated epidemic with $R_t = 2$ throughout this period (which was estimated would have resulted in 59,900 (26,800-112,800, 95% UI) deaths. However, these numbers do not account for the effects of healthcare services becoming overwhelmed. **Figure 3.5C** shows how the unmitigated spread of COVID-19 in districts in Java Island could overwhelm healthcare facilities. The lines denote the median number of hospital beds available per COVID-19 needing hospitalisations. Negative values of the number under the unmitigated epidemic scenario during the first few months of the epidemic mean there were no adequate resources to treat COVID-19 cases during that time properly. However, this analysis assumed all hospital beds were available for COVID-19 cases. In reality, dedicated healthcare facility beds and resources for COVID-19 cases were much lower than the total capacity of the healthcare facilities. Overwhelmed healthcare facilities would have impacted mortality both directly and indirectly. This impact would likely have been sizable given the wider spread to more rural settings with more inadequate healthcare provision in our unmitigated scenario (**Figure 3.5D** and **3.5E**).

Finally, the baseline scenario simulations increasingly over-predicted deaths in most provinces during the AKB (post the first PSBB). Model-simulated COVID-19 cases (**Figure S3.1**) also show similar trends, except in Jakarta, where the model constantly underestimates the reported cases. This overprediction, in general, is in line with the previous chapter's results, suggesting a

decoupling of within-province mobility from virus transmissibility over that period. Furthermore, sensitivity analysis shows that the model simulations are sensitive to the assumed reduction in rural transmission (**Figure S3.2**). **Figure S3.3** also shows that the model was not sensitive to a stricter assumption on the relationship between within- and inter-district mobility.

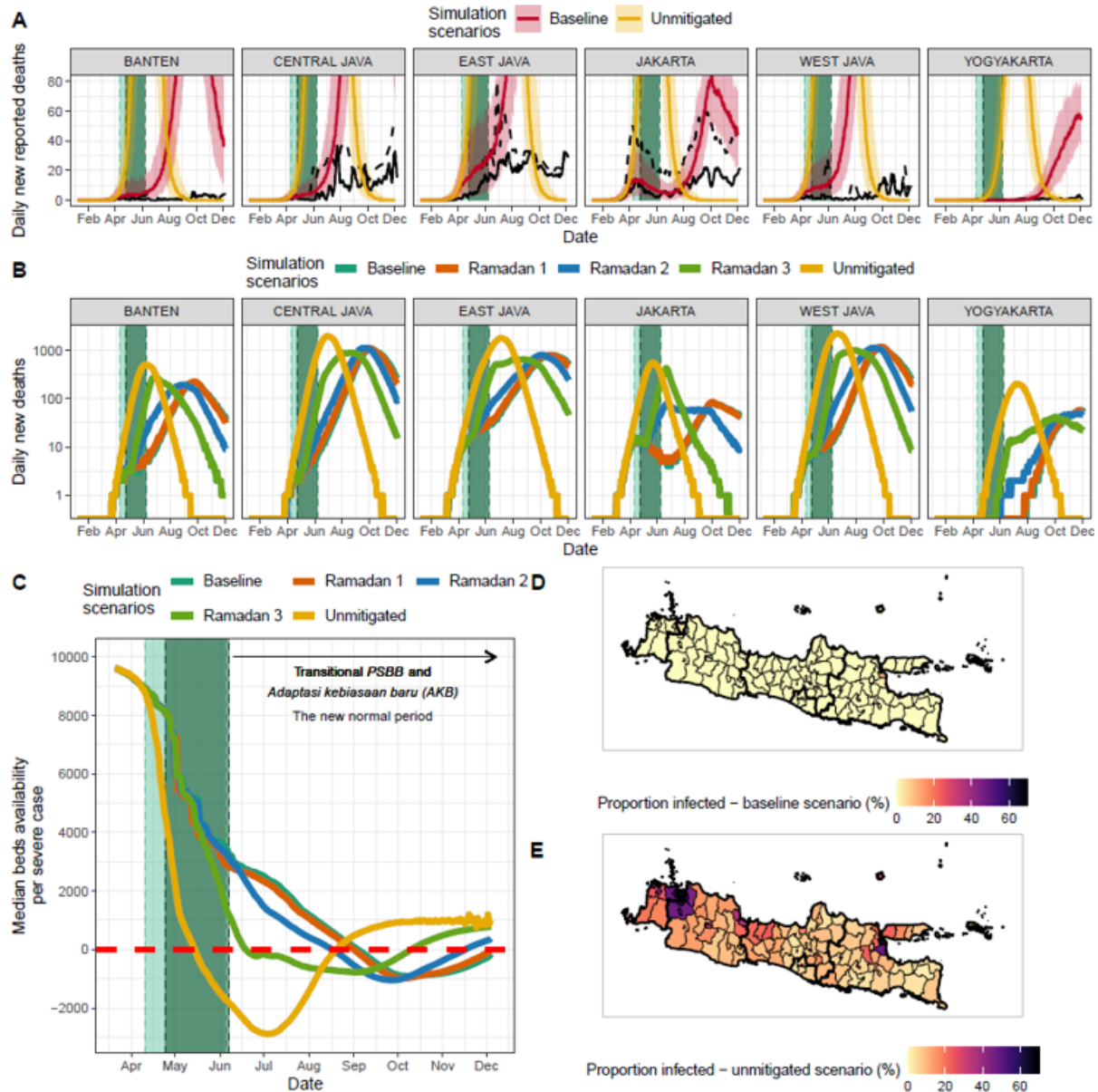


Figure 3.5. Metapopulation model simulation results. A) Comparison of model simulations in the baseline scenario (red lines and their shaded 95% uncertainties ranges) and unmitigated scenario (yellow lines and their shaded 95% uncertainties ranges), and daily confirmed (solid black lines) and suspected (dashed black lines) deaths from COVID-19. B) Model simulations in five different scenarios: 1) Baseline scenario as shown in Figure 3.5A, 2) Ramadan counterfactual 1 where it is assumed that there are no movement restrictions during the Ramadan period and R_t values are similar to the baseline scenario, 3) Ramadan counterfactual 2 where it is assumed that there are no movement restrictions during the Ramadan period

and R_t values are 75% of each district's R_0 value, 4) Ramadan counterfactual 3 where it is assumed that there are no movement restrictions during the Ramadan period and R_t values are each district's R_0 value and 5) Unmitigated scenario where no interventions since the beginning of the epidemic are assumed. C) Median hospital bed availability per severe COVID-19 case over time, based on different simulation scenarios. D) Proportion of people infected based on the actual scenario up to 31st May 2020 (before AKB/the 'new normal') at the district level. E) Proportions of people infected based on the unmitigated scenario up to 31st May 2020 (before AKB) at the district level. Light green shaded areas denote periods of PSBB, while the dark green shaded areas represent the period of Ramadan domestic travel restrictions.

Table 3.4. The total number of estimated deaths, based on model simulations of the baseline and unmitigated scenario.

Province	Confirmed deaths 13 th -31 st May (WHO Indonesia situation report 10)	Suspected deaths 13 th -31 st May (WHO Indonesia situation report 10)	Baseline model scenario deaths 13 th -31 st May	Confirmed deaths up to 31 st May	Suspected deaths up to 31 st May (provincial data collated by KawalCOVID19)	Baseline model scenario deaths up to 31 st May	Unmitigated counterfactual deaths up to 31 st May	Averted deaths up to 31 st May (unmitigated – baseline)
Jakarta	74	447	158 (47-333)	520	2,435	810 (292-1777)	16,356 (7,896-21,593)	15,560 (7,567-19,691)
West Java	46	351	197 (55-525)	135	653	525 (149-1,368)	19,733 (5,682-39,876)	19,151 (5,516-38,400)
Central Java	4	269	88 (36-216)	66	666	203 (67-511)	6,321 (2,147-16,052)	6,068 (2,056-15,485)
Yogyakarta	0	1	2 (0-8)	9	29	6 (1-33)	401 (138-1,097)	397 (132-1,088)
East Java	241	458	437 (98-944)	395	1,127	1,091 (226-2,646)	12,182 (3,625-20,800)	10,997 (3,277-27,045)
Banten	13	47	82 (20-224)	67	332	229 (66-711)	7,302 (2,180-14,732)	7,0759 (2,111-14,141)
Java Island total	378	1,638	983 (360-1,930)	1,192	5,242	2,912 (1,109-5,851)	59,896 (26,787-112,795)	57,030 (24,843-105,378)

* Values inside the brackets denote 95 percentile range of simulations. Suspected deaths are a combination of confirmed and probable COVID-19 deaths.

3.4 Discussions

The results in this chapter show how movement restrictions during the first wave of the COVID-19 epidemic in Indonesia attenuated the spread of COVID-19 to the rural areas of Java Island, thus preventing a much larger potential burden in those areas due to older populations and lower healthcare capacities. If the movement restrictions were not in place, especially during Ramadan, to prevent people from doing their traditional ‘mudik’ practice, model simulations estimated that the deaths due to COVID-19 could be 20 times higher than the model expected when restrictions were in place. However, the model constantly underestimated reported cases in Jakarta, indicating that calibration to deaths data may need to be closer to the suspected deaths than confirmed deaths. The results shown here may have underestimated the overall potential impact of the first wave of the COVID-19 epidemic on Java Island, but qualitatively, the substantial impact of restrictions relative to an unmitigated epidemic is highly likely to be robust to this uncertainty. Moreover, those figures did not account for the potential direct and indirect effects of overwhelmed healthcare facilities if the disease spread to rural areas of Java. These further highlight the importance of NPIs, especially in delaying and slowing the spread of COVID-19, during the first waves of the pandemic across the globe, when vaccines and therapeutic medicines were still under development.

NPIs implemented during the first wave of the epidemic and the Ramadan period in 2020 could only attenuate the spread of COVID-19. In provinces other than Jakarta, where within-district population movement reductions were relatively lower, the increasing pattern of COVID-19 cases and deaths already started in May during Ramadan before the lifting of PSBB restrictions by the central government in early June. This increasing pattern during PSBB may be a sign that seeding of cases already occurred before restrictions were in place, similar to the analysis of inter-district movement restrictions in China (Quilty et al., 2020), or the restrictions in place were not perfect in preventing people from performing ‘mudik’. However, the increasing trajectory was still slower compared to what the model expected if there were no restrictions, as the imposed restrictions managed to reduce population contact patterns and further seeding of COVID-19 cases from districts with higher burdens on the island. Later, after the easing of restrictions in June, surges of COVID-19 cases in East Java led to overwhelmed healthcare facilities (Syakriah, 2020b), further highlighting the difficulties in controlling the epidemic while relying only on NPIs.

Due to the broad scale of movement restrictions implemented nationwide, it is difficult to provide empirical counterfactual data that support the impact of the restrictions, especially during Ramadan in Indonesia. However, in 2021, ‘mudik’ restrictions were implemented in a shorter period (two weeks) and later in the month of Ramadan (in the third week of Ramadan) (Cabinet Secretariat of the Republic of Indonesia, 2021b), prompting experts saying that they

were less effective compared to the previous year's due to people already travelled before the restrictions were imposed (BBC News Indonesia, 2021). In the following months after Ramadan, Indonesia faced its deadliest COVID-19 wave, with shortages of oxygen and hospital beds to care for COVID-19 patients reported across the country (Cahya & Ratcliffe, 2021). The impact of this wave may also be exacerbated by the fact that the main variant circulated during the wave was the Delta variant which has higher transmissibility compared to the original variant during the first wave (Hart et al., 2022; B. Li et al., 2022; Liu & Rocklöv, 2021). However, this comparison may illustrate how large-scale movements affect the spatial spread and the speed of transmission at the national scale in a country like Indonesia.

This chapter has limitations related to the data and methods for analysis. First, I used a relatively old CDRs dataset to estimate population mobility. Second, the mobility datasets might be biased more toward the urban population with higher ownership (Badan Pusat Statistik, 2012). However, due to no other sources of data available to estimate district-level population mobility, the estimates from these data can still be used with careful interpretations. Third, I did not account explicitly for the potential impact of overwhelmed healthcare facilities due at the district level on the burden of COVID-19 on the population. This is due to the difficulty in estimating the direct and indirect effects of the overwhelmed healthcare facilities and the unavailability of district-level data on dedicated COVID-19 isolation and ICU beds in each district. Fourth, the decoupling of population mobility and transmission means the metapopulation model results were only reliable for estimating the spread before the lifting of restrictions in June. Finally, no district-level data on confirmed and suspected COVID-19 deaths is available at the time of analysis to validate the model. Validations were only possible at the province level.

3.5 Conclusions

In this chapter, I developed a metapopulation model that could simulate the spatial spread of COVID-19 at the district level in Java Island during the first wave of the COVID-19 epidemic in Indonesia. Using the model, a few epidemic scenarios were explored, including what could happen if the between-district mobility during the festive Ramadan month remained the same as the previous years during the wave of the COVID-19 epidemic. Simulations found that if movements remained the same as in previous years without restrictions, the deaths due to COVID-19 could reach 20 times the baseline scenario where COVID-19 restrictions were in place. Furthermore, this burden would likely be higher if the impact of the likely overwhelming capacity in healthcare facilities, especially in the rural areas of Java Island, were accounted for. In summary, these results highlight the importance of NPIs implemented during the first wave of the COVID-19 epidemic in Java Island in slowing the spread of COVID-19 to the rural areas in Java Island and thus preventing potentially catastrophic epidemics during the critical

period of the pandemic where adequate preventive and therapeutic measures were still lacking.

Chapter 4: Estimating the current level of infections and future scenarios of COVID-19 in Java Island, in the prospect of vaccination rollouts

This chapter concerns analysis carried out to explore future trajectories of the SARS-CoV-2 transmission in the Java Island population at different stages of the first year of the COVID-19 pandemic in Indonesia. Such potential future trajectories, accounting for various future transmission scenarios, were important to consider, given the planned COVID-19 national vaccination rollouts in early 2021. The projected number of people who die in the future due to the virus could be people whose lives could be saved by the newly available vaccines. However, future trajectories generated by mathematical models are also sensitive to the assumed current burden of the virus, which is also related to the immunity already accumulated in the population. Given the uncertainty in the burdens estimated using different surveillance metrics, as shown in the past chapters, this chapter also focused on analysing the differences between burdens estimated based on confirmed and suspected COVID-19 deaths. The Imperial College London COVID-19 response team developed the mathematical model used in this chapter, which was then implemented using the `squire` package in R. Oliver J. Watson helped develop and run the model's calibration process to Java Island data. I prepared the data for the model calibration process, designed the future transmission scenarios, ran the data and model simulation analysis, and produced all the graphs.

4.1 Introductions

4.1.1 Background

In the final quarter of 2020, interim analyses of the ongoing phase 3 COVID-19 vaccine trials (Callaway, 2020; Zhang, 2020) produced very positive results suggesting that vaccination could become a highly useful tool in combating the burden of COVID-19 and a future without the need for stringent NPIs. More than ten vaccine candidates from various pharmaceutical companies were developed using different platforms (Kyriakidis et al., 2021). Some of the notable ones are Pfizer BioNTech and Moderna, who used mRNA technology (National Institutes of Health, 2020; Pfizer, 2020); Oxford-AstraZeneca, who used an adenovirus viral vector platform (AstraZeneca, 2020); and Sinovac, who used a more traditional inactivated virus platform for their vaccines (Reuters, 2020b). In December 2020, the United Kingdom became the first country to start its national COVID-19 mass vaccination program, prioritising healthcare workers and the elderly in the early phase of the program (Ledford et al., 2020).

When this study was conducted, Indonesia was about to start its national mass COVID-19 vaccination program at the beginning of 2021 (Widianto, 2021b).

Initial results of trials of COVID-19 vaccines showed how the severity of COVID-19 infection, in terms of symptoms and needs for hospitalisation, was reduced significantly (AstraZeneca, 2020; National Institutes of Health, 2020; Pfizer, 2020). This reduction in severity, especially in vulnerable populations, indicated that many COVID-19 deaths could be averted if vaccination programs were implemented successfully (Lipsitch & Dean, 2020). Furthermore, there was evidence that immunity induced by the vaccines could also substantially reduce the transmission potential of the virus in the population (Levine-Tiefenbrun et al., 2021), leading to the further impact of such campaigns over and above the direct protection from disease conferred by vaccination. However, given the inevitable challenges of achieving universal coverage through national mass vaccination, which subsequently proved to be exacerbated by supply restrictions by vaccine manufacturers, the lack of cold chain infrastructures in some areas of the country, and misinformation that caused vaccine hesitancy (Arifin & Anas, 2021; Kuipers & Mujani, 2022; Surianta, 2021), measures that aimed to reduce virus transmission in the population were still needed, especially to ensure that those who needed the vaccines received it prior to being exposed to infection.

For public health programs such as mass vaccination campaigns, it is quite common to use mathematical models to project their future impacts (E. C. Lee et al., 2019; Portnoy et al., 2021). For models that may be used to inform policy, it is important to ensure that the model is properly calibrated through a model calibration process. This calibrated model can then be used to simulate, for example, the prevalence or incidence trends of the disease of interest. The model calibration process itself is defined as a process of estimating uncertain model input values, which may not be directly observable (i.e., disease transmission parameters), to match some pre-specified objectives from data (i.e., disease surveillance data, prevalence estimates from surveys) (Ryckman et al., 2020; Zang et al., 2020). Hence, simulated trajectories generated by the models may be sensitive to the data used for the calibration process, which is important to consider when interpreting disease model outputs, especially those related to the public health impact of intervention programs.

In **Chapter 2**, I have shown how the lack of testing during the initial phase of the pandemic may have underestimated the ‘true burden’ of the pandemic in provinces in Java, especially when comparing the reported cases and deaths data to the suspected deaths that came from the C19P burials in Jakarta. In this chapter, I explored further how mathematical model calibrations to these different datasets might produce different estimates of disease burden that would affect future trajectories produced by the model, primarily due to the differential levels of previous spread and population-level immunity such differences in burden would

imply. I then discuss the implications of these simulations for the, then future, success of any forthcoming vaccination campaign in 2021.

4.1.2 Aims

In this chapter, the analysis focused on applying an established SARS-CoV-2 transmission model. I aimed to:

1. Estimate province-level attack rates based on confirmed COVID-19 deaths data and suspected COVID-19 deaths data.
2. Compare the differences in the magnitude of the estimated burden based on confirmed and suspected COVID-19 deaths.
3. Simulate future trajectories of COVID-19 burdens, accounting for different intervention scenarios, in the context of vaccination rollouts in 2021.

4.2 Data and methods

4.2.1 Data

4.2.1.1 Epidemiological data sources

Similar to previous chapters, reported confirmed COVID-19 deaths and suspected deaths (C19P funerals) data for the Jakarta province were obtained from the official Jakarta COVID-19 data monitoring website (<https://corona.jakarta.go.id/id/data-pemantauan>) (Jakarta Provincial Health Department, 2020). For the five other provinces in Java, reported COVID-19 deaths data were obtained from an independently curated online spreadsheet by a crowdsourcing organisation KawalCOVID19 (kcof.id/daftarpositif) based on the daily publication by the Indonesia COVID-19 National Task Force (Indonesia COVID-19 Task Force, 2020; KawalCOVID19, 2020). In addition, the weekly number of deaths of suspected and probable COVID-19 cases, which represent probable deaths of COVID-19, were obtained from WHO Indonesia situation reports 13-36 (WHO Indonesia, 2020). These reports covered the period of 1st June 2020 to 29th November 2020. These collated weekly death data for each province are shown in **Figure 4.1**.

4.2.1.2 Dedicated COVID-19 isolation beds and ICU beds data

Data for the capacity of the dedicated COVID-19 isolation beds and ICU beds were obtained from a healthcare capacity report by the Ministry of Health of the Republic of Indonesia in August 2020 (Ministry of Health of the Republic of Indonesia, 2020a).

4.2.2 Methods

4.2.2.1 Estimating the daily number of suspected COVID-19 deaths in Java provinces

The daily number of suspected COVID-19 deaths in Jakarta is available publicly through the province's COVID-19 data monitoring website, represented by the C19P funerals data. However, such data was not publicly available for other provinces in Java. WHO Indonesia collated and published weekly data on confirmed and probable COVID-19 deaths for all provinces in Java through their weekly situation reports (WHO Indonesia, 2020). Those confirmed and probable COVID-19 deaths combined, by definition, are equivalent to the suspected COVID-19 deaths as defined for Jakarta's C19P funerals data. However, in reality, those are still subject to whether those developing symptoms seek care. I developed a statistical model to convert the weekly suspected deaths data into daily suspected deaths data for the five provinces in Java other than Jakarta.

For all days from 1st March 2020 to 7th December 2020, daily probable deaths in five Java provinces other than Jakarta were generated probabilistically from confirmed deaths. Firstly, the daily confirmed deaths in each province were aggregated over a weekly period ($D_{i,t}$ with t as the weekly time window). Then, the overall proportion of confirmed deaths from suspected COVID-19 deaths for each province (ρ_i with i as each province index) was calculated from the collated suspected deaths data. Finally, for each weekly time window t , I simulated the number of probable deaths ($O_{i,t}$) in each province ten times, assuming a Negative Binomial distribution:

$$O_{i,t} = NB(D_{i,t}, \rho_i)$$

where $D_{i,t}$ is the weekly number of confirmed COVID-19 deaths in province i at week t . This simple equation modelled the weekly number of probable COVID-19 deaths, $O_{i,t}$, based on the weekly observed confirmed COVID-19 deaths, $D_{i,t}$, given the proportion of confirmed deaths among all suspected COVID-19 deaths, ρ_i .

Then, for each simulated $O_{i,t}$, I simulated the spread of the weekly total estimated probable deaths into daily estimated probable deaths using Multinomial distribution, assuming an equal probability of probable deaths to occur on each day during the week:

$$o_{i,t} = Multinom(O_{i,t}, \pi)$$

where π is a vector of length seven that has 1/7 for the value of its every component, and $o_{i,t}$ is a vector of daily simulated probable COVID-19 deaths at province i within week t ($O_{i,t} = \sum o_{i,t}$).

These simulations generated 100 samples of estimated daily probable COVID-19 deaths in each province. The samples of the estimated daily suspected deaths were acquired by adding

these simulated values of the daily probable deaths to the daily reported confirmed COVID-19 deaths in each province. Finally, the daily number of suspected COVID-19 deaths was defined as the daily number of C19P funerals for the Jakarta Province and the median of the estimated daily suspected COVID-19 deaths for the other provinces in Java.

4.2.2.2 SARS-CoV-2 age-structured transmission model

I used the SEIR modelling framework and structure developed to simulate the dynamics of a SARS-CoV-2 outbreak, its healthcare demand over time, and its resultant mortality as in Walker et al. and Imperial College COVID-19 Low- or Middle-Income Countries (LMICs) Reports (MRC Centre for Global Infectious Disease Analysis, 2020; Walker et al., 2020). The model is an age-structured SEIR model, explicitly incorporating mixing patterns across and between different age groups and reflecting the progression of individuals infected by the virus through the different disease severity pathways.

The compartments representing the model structure are shown in **Figure 4.2**. S represents susceptible populations, E represents exposed individuals who are still in their latent periods, I represents the progression of the exposed individuals (E) into their disease state (or when they are supposed to show symptoms or no symptoms at all), and R represents recovered individuals. The I compartment is further divided into I_{mild} which represents individuals with mild symptoms who did not require hospitalisations (including those who were asymptomatic), and I_{case} which represents individuals presenting symptoms requiring hospitalisations. The individuals who require hospitalisations I_{case} were further separated into those who only need regular hospital beds ($I_{hospital}$) and those who need critical care beds (I_{ICU}). Recovered non-critical individuals ($I_{hospital}$) will progress to becoming recovered individuals (R). While those who need critical care (I_{ICU}) will slowly progress to I_{rec} after their critical period passes, occupying regular hospital beds before becoming recovered individuals (R).

Furthermore, the model also explicitly tracks individuals' disease severity and treatment options. The individuals are assumed to access treatment if it is available. The decision trees for the treatment cascade are shown in **Figure 4.3**. The process of tracking individuals throughout their infection pathways is as follows. $S(t, a)$ denotes the susceptible individuals in age group a at time t . $E_1(t, a)$ and $E_2(t, a)$ are two sequential latent periods of infection. $I_{mild}(t, a)$ are infected individuals who are either symptomatic or asymptomatic but do not require hospitalisation. $I_{case,0}(t, a)$ and $I_{case,1}(t, a)$ are two sequential states for symptomatic infections that will subsequently require hospitalisation. $I_{Hospital,1}(t, a)$ and $I_{Hospital,2}(t, a)$ are two sequential states for infections requiring general hospital beds. $I_{ICU,1}(t, a)$ and $I_{ICU,2}(t, a)$ are two sequential states for infections requiring ICU beds. $I_{Rec,1}(t, a)$ and $I_{Rec,2}(t, a)$ are two sequential states for infections requiring general hospital beds after recovering from ICU.

$R(t, a)$ are recovered individuals who are immune to reinfection, and $D(t, a)$ are individuals who died from the disease.

Additionally, the model captures the hospital capacity constraints by further splitting $I_{Hospital,i}(t, a)$ and $I_{ICU,i}(t, a)$ states ($i = 1, 2$) to track those who either receive (1) or do not receive (0) their general hospital or ICU beds and whether they die (0) or recover (1) (see notations to the right side of the compartment in **Figure 4.3**). This would allow for different duration of stays to be captured by the model depending on the disease outcome. For example, the state that tracks an individual requiring a general hospital bed but does not receive it and proceeding to die is $I_{Hospital,i}(t, a, 0, 0)$, whilst the state that tracks individuals requiring a general hospital bed, receiving it, and proceeding to recover is $I_{Hospital,i}(t, a, 1, 1)$. In the full equations (Walker et al., 2020; Watson et al., 2021), the Kronecker Delta function $\delta(\cdot)$ is used to capture capacity constraint, with the value equal to one if there is a capacity (of either general hospital or ICU bed) and 0 otherwise.

The social contact mixing matrix, $c(a, a')$, representing the rate of contacts between individuals in age groups a and a' , was used to represent the contacts between age groups in the model. For all provinces in Java, the social contact matrix used the value estimated for Shanghai in China. The model does not account for births, deaths, and aging, as the analysis focused only on short-term dynamics. The population age structures for each province represent their states in 2020. The model was implemented using the `squire` package v0.5.8 in R. The deterministic version of the model was used for the analysis, with five initial seeds in the exposed infection class randomly distributed to age groups. The model parameter symbols, descriptions, and values, based on model parameters used in the `squire` package v.0.5.8 are shown in **Table S4.1**.

4.2.2.3 Fitting SARS-CoV-2 transmission model to COVID-19 deaths data to estimate province-level attack rates in Java

Using the framework developed in the Imperial College COVID-19 LMIC reports (MRC Centre for Global Infectious Disease Analysis, 2020; Walker et al., 2020; Watson et al., 2021), the SARS-CoV-2 transmission model was fitted to both the daily COVID-19 confirmed deaths and the daily COVID-19 suspected deaths data for each province in Java, estimating both a province-specific R_0 and epidemic start date. Furthermore, to provide model fits that are agnostic to the mobility profiles in each province, we model the time-varying reproduction number, R_t , using a series of pseudo-random walk parameters, which alter the transmission rate every two weeks, with R_t given by:

$$R_t = R_0 \cdot f(-\rho_1 - \rho_2 \dots - \rho_n)$$

where $f(x) = 2 \exp(x)/(1 + \exp(x))$, i.e., twice the inverse logit function, which has been used in previous models to capture the impact of mobility data on transmission (Unwin et al., 2020). Each ρ parameter is introduced two weeks after the previous parameter, capturing changes in transmission over time. Specifically, each ρ parameter is set equal to 0 for each day before its start date. For example, ρ_1 is the change in transmission, which is set to start at the beginning of the epidemic. The estimated value for ρ_1 is then maintained for all future time points. ρ_2 is the second change in transmission, which starts 14 days after the epidemic start date, i.e., is equal to 0 prior to this. Finally, the last mobility-independent change in transmission, ρ_n , is maintained for the last four weeks prior to the current day to reflect our inability to estimate the effect size of this parameter due to the approximate 21-day delay between infection and death (Walker et al., 2020).

Model fittings were done contemporaneously during the pandemic using the data available up to the time of the fitting process; first, using the data up to 2nd September 2020 (before the 2nd PSBB in Jakarta was imposed in mid-September), and second, using the data up to 7th December 2020. Based on the fitted models in all provinces considering different types of death data, the attack rates at the province level and Java Island level were estimated. Then some scenarios of future projections were simulated. This represents a real-time analysis and projections of an epidemic based on currently available data, which was similarly done, as an example, in the analysis of SARS-CoV-2 transmission in French Guiana (Andronico et al., 2021).

4.2.2.4 Future projections of COVID-19 scenarios at the province-level in Java

Using the fitted models to both confirmed and suspected deaths data, several future projection scenarios were explored based on the assumed values of the reproduction number under control, R_c . R_c is defined as the average number of secondary infections within an entirely susceptible population but incorporating the impact of NPIs (equivalent to R_t but not incorporating the effects of population-level immunity such that $R_0 > R_c > R_t$). Moreover, as with R_0 , $R_c > 1$ can lead to $R_t < 1$ and a declining epidemic if sufficient levels of naturally acquired immunity exist within the population.

The forward projection scenarios and their outputs are described in **Table 4.1**. Three main scenarios were considered: ‘unmitigated’, ‘current trajectory’, and ‘suppression’. In the ‘unmitigated’ scenario, the forward projection R_c was assumed to be 2.00, reflecting the value of SARS-CoV-2’s basic reproduction number (R_0) at the early stage of the pandemic (Flaxman et al., 2020b). In the ‘current trajectory’ and ‘suppression’ scenarios, the initial R_c values for the forward projections were assumed to be 1.25 and 0.75, respectively. These values represented the current outbreak trajectory at that time and the situation where transmission was being suppressed. In both scenarios, the transmission was assumed to ‘return to normal’

at one point in the future, meaning the R_c for the forward projections returned to 2.00. Additionally, sub-scenarios for 'return to normal' were simulated, assuming that 'return to normal' happened at the beginning of February, March, April, May, and June. Finally, for sensitivity analysis, forward projections were also made assuming R_c in the 'unmitigated' scenario and after 'return to normal' to be 3.00, representing the emergence of a more transmissible variant of SARS-CoV-2.

For each scenario simulation, I calculated the potential future impact of mass vaccination campaigns and the healthcare demand due to COVID-19 given the scenarios of SARS-CoV-2 transmission. To assess the potential future impact of vaccination campaign, I devised two metrics; they are the proportion of lives lost before 'return to normal' and the number of lives remaining to be saved after 'return to normal'. The schematics on how to calculate these metrics are shown in **Figure 4.4**. Example trajectories of all provinces are shown in **Figure S4.7**. The proportion of lives lost represents the proportion of simulated COVID-19 deaths before the transmission 'return to normal' from the total simulated COVID-19 deaths in an unmitigated scenario. A low proportion of lives lost means there were still many lives that vaccines could save in the future. The number of lives remaining to be saved can also be defined as the number of deaths that can still be averted (by vaccines). This metric represents the total number of COVID-19 deaths simulated after the transmission 'return to normal'. The higher the value of this metric, the better the strategy implemented before 'return to normal' in keeping the value of vaccination programs high.

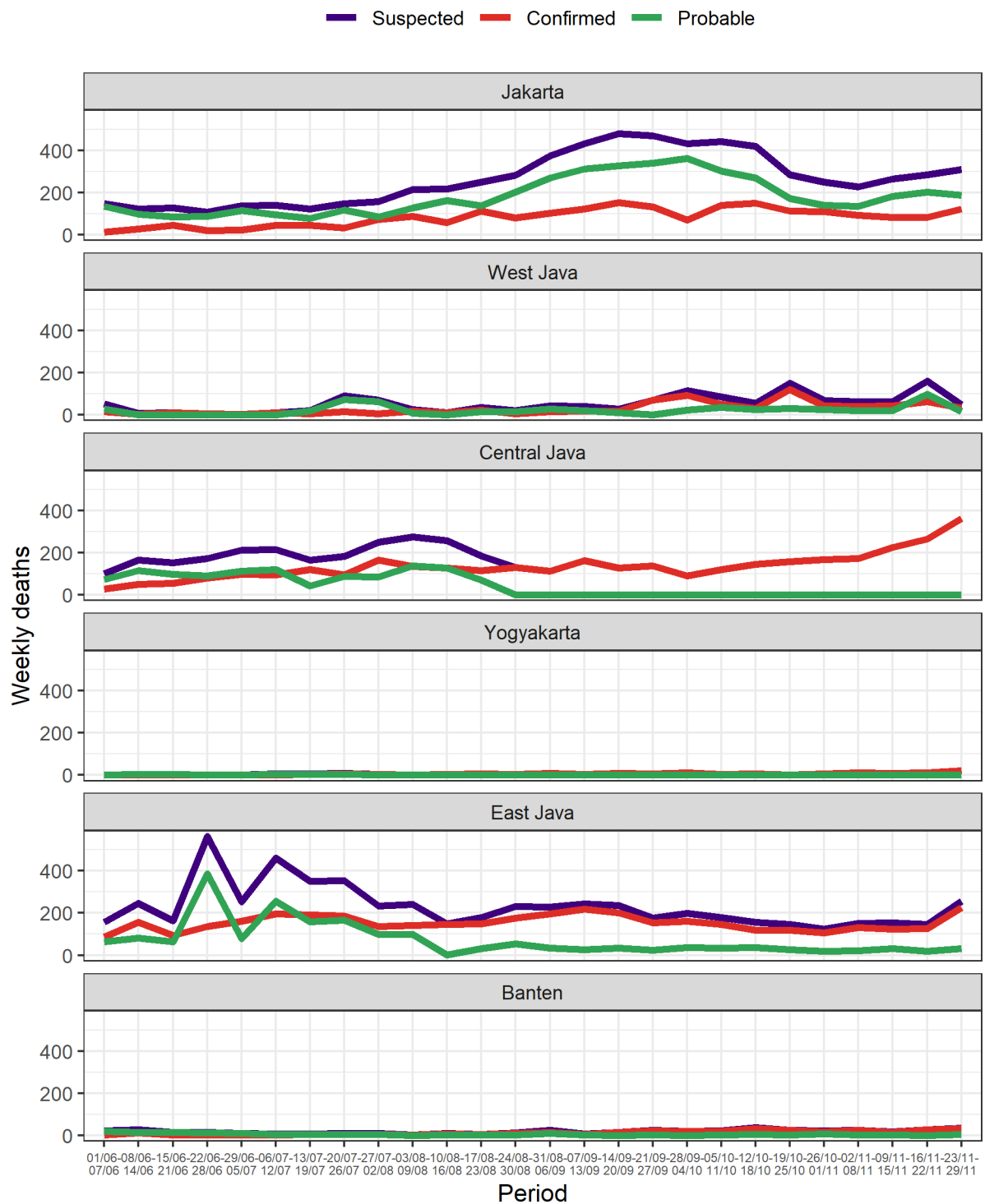


Figure 4.1. Weekly aggregated confirmed and probable deaths in all six provinces of Java. Suspected COVID-19 deaths shown as purple lines are defined as the total of confirmed (red) and probable (green) COVID-19 deaths. Data collated from WHO COVID-19 Indonesia situation reports 13-36 (WHO Indonesia, 2020).

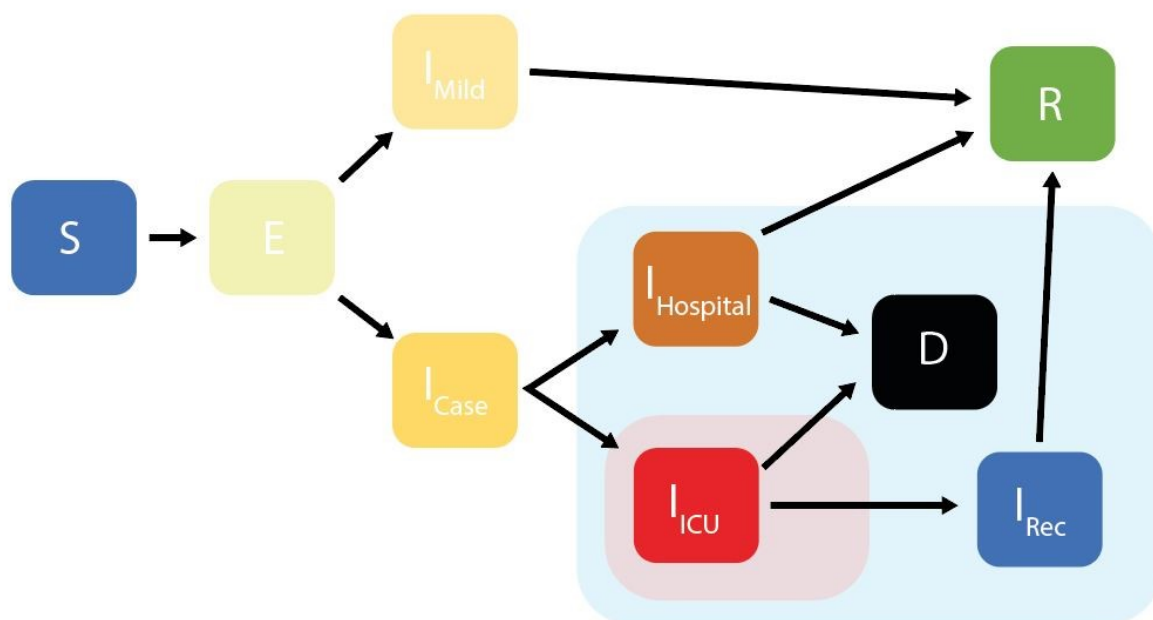


Figure 4.2. Compartmental model structure for the age-structured SARS-CoV-2 transmission model. This figure is adapted from the Imperial College COVID-19 LMICs Reports page (MRC Centre for Global Infectious Disease Analysis, 2020). The pale blue box shows compartments related to hospitalisations that occupy an available hospital bed. The pale red box shows the compartment related to hospitalisations that occupy an ICU hospital bed.

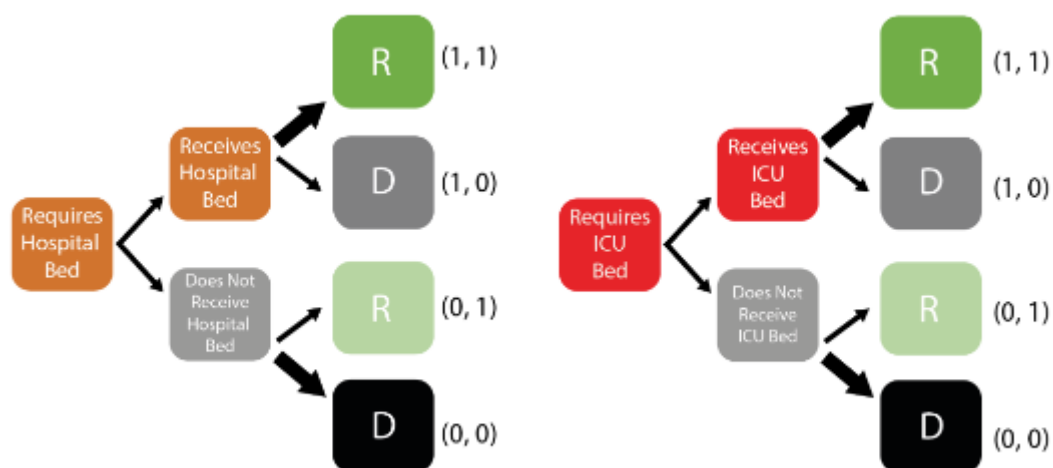


Figure 4.3. Decision tree cascade to model excess mortality associated with healthcare capacity being exceeded. The modelling framework explicitly tracks healthcare capacity and availability. At each timestep, individuals needing general hospital or ICU beds are assigned to available beds, independently of age. Those receiving a bed are subject to a lower probability of death than those not. This figure is adapted from the Imperial College COVID-19 LMICs Reports page (MRC Centre for Global Infectious Disease Analysis, 2020).

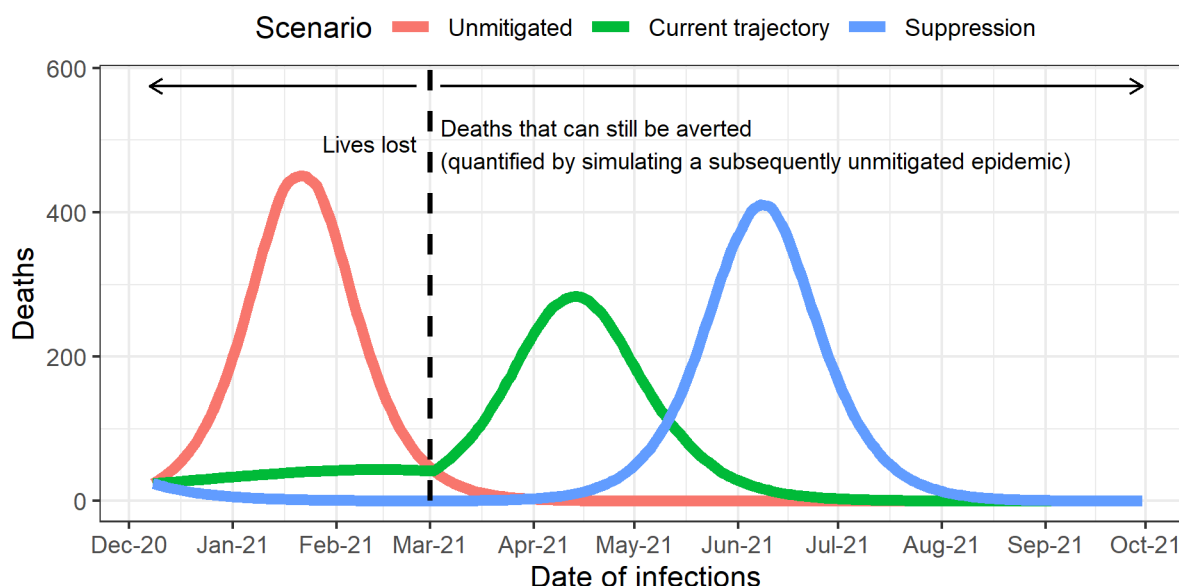


Figure 4.4. An illustration of future scenario projections and how to define the number of lives lost and the number of deaths that can still be averted after a certain time point. The graph shows simulations based on a model fitted to confirmed COVID-19 deaths in Jakarta, which subsequently ‘returning to normal’ on 1st March 2021.

Table 4.1. List of future projection scenarios for province-level simulations.

Projection scenarios to calculate lives lost and remaining to save		
Scenario name	Details	Output
Unmitigated ($R_c = 2.00$) – main text	Based on the model fitted to confirmed and suspected deaths data, forward projections were simulated assuming the $R_c = 2.00$ from 8 th December 2020 onwards.	Projected number of lives lost and remaining to save (Figure 4.7)
Current trajectory ($R_c = 1.25 \rightarrow 2.00$) – main text	Based on the model fitted to confirmed and suspected deaths data, forward projections were simulated assuming the $R_c = 1.25$ (a representative value for current outbreak trajectory) from 8 th December 2020 onwards. Transmission then ‘returns to normal’ at the levels earlier in the pandemic ($R_c = 2.00$), simulated in the beginning of February, March, April, May, and June.	Projected number of lives lost and remaining to save (Figure 4.7)
Suppression ($R_c = 0.75 \rightarrow 2.00$) – main text	Based on the model fitted to confirmed and suspected deaths data, forward projections were simulated assuming the $R_c = 0.75$ (a representative value for a transmission suppression strategy) from 8 th December 2020 onwards. Transmission then ‘returns to normal’ at the levels earlier in the pandemic ($R_c = 2.00$), simulated in the beginning of February, March, April, May, and June.	Projected number of lives lost and remaining to save (Figure 4.7)

Unmitigated ($R_c = 3.00$) – sensitivity analysis	Based on the model fitted to confirmed and suspected deaths data, forward projections were simulated assuming the $R_c = 3.00$ (assuming a higher basic reproduction number of the virus than the main simulation scenarios) from 8 th December 2020 onwards.	Projected number of lives lost and remaining to save (Figure S4.8)
Current trajectory ($R_c = 1.25 \rightarrow 3.00$) – sensitivity analysis	Based on the model fitted to confirmed and suspected deaths data, forward projections were simulated assuming the $R_c = 1.25$ (a representative value for current outbreak trajectory) from 8 th December 2020 onwards. Transmission then ‘returns to normal’ at the levels earlier in the pandemic ($R_c = 3.00$), simulated in the beginning of February, March, April, May, and June.	Projected number of lives lost and remaining to save (Figure S4.8)
Suppression ($R_c = 0.75 \rightarrow 3.00$) – sensitivity analysis	Based on the model fitted to confirmed and suspected deaths data, forward projections were simulated assuming the $R_c = 0.75$ (a representative value for a transmission suppression strategy) from 8 th December 2020 onwards. Transmission then ‘returns to normal’ at the levels earlier in the pandemic ($R_c = 3.00$), simulated in the beginning of February, March, April, May, and June.	Projected number of lives lost and remaining to save (Figure S4.8)

Projection scenarios to assess pressure on healthcare capacity		
Scenario name	Details	Output
$R_c = 0.75 \rightarrow 2.00$ (Susp.)	Based on the model fitted to suspected deaths data, forward projections were simulated assuming the R_c dropped to 0.75. Transmission returns to levels observed at the beginning of the outbreak (i.e., $R_c = 2$) due to behaviour change once burden declines to low levels (total deaths for 7 consecutive days < 7).	Daily number of deaths (Figure S4.9)
$R_c = 0.75 \rightarrow 1.25$ (Susp.)	Based on the model fitted to suspected deaths data, forward projections were simulated assuming the R_c dropped to 0.75. Transmission returns to current levels observed during AKB (i.e., $R_c = 1.25$) due to behaviour change and sustained intervention policies once burden declines to low levels (total deaths for 7 consecutive days < 7).	Daily number of deaths (Figure S4.9)
$R_c = 0.75 \rightarrow 1.25$ (Conf.)	Based on the model fitted to suspected deaths data, forward projections were simulated assuming the R_c dropped to 0.75. Transmission returns to current levels observed during AKB (i.e., $R_c = 1.25$) due to behaviour change and sustained intervention policies once burden declines to low	Daily number of deaths (Figure S4.9)

	levels (total deaths for 7 consecutive days < 7).	
$R_c = 1.25 \rightarrow 2.00$ (Susp.)	Based on the model fitted to suspected deaths data, forward projections were simulated assuming the R_c stayed at the current estimated level in all provinces (1.25 - within the range of the most recent point estimates in Figs. S4.1 & S4.2). Transmission returns to levels observed at the beginning of the outbreak (i.e., $R_c = 2$) due to behaviour change once burden declines to low levels (total deaths for 7 consecutive days < 7).	Daily number of deaths and healthcare demand (Figure S4.9)
$R_c = 1.25 \rightarrow 2.00$ (Conf.)	Based on the model fitted to confirmed deaths data, forward projections were simulated assuming the R_c stayed at the current estimated level in all provinces (1.25). Transmission returns to levels observed at the beginning of the outbreak (i.e., $R_c = 2$) due to behaviour change once burden declines to low levels (total deaths for 7 consecutive days < 7).	Daily number of deaths and healthcare demand (Figure S4.9)
$R_c = 2.00$ (Susp.)	Based on the model fitted to suspected deaths data, forward projections were simulated assuming the R_c increased to the initial level of 2.00 in all provinces, representing 'back-to-normal' condition.	Daily number of deaths (Figure S4.9)

4.3 Results

Figure 4.5 shows the province-level daily confirmed COVID-19 deaths in all provinces on Java Island. The figure also shows the daily suspected COVID-19 deaths for each province, the C19P funerals for Jakarta, and the simulated values for other provinces. The total number of confirmed and suspected deaths up to the two model fitting dates, 2nd September 2020 and 7th December 2020, are shown in **Table 4.2**.

Table 4.2. Total confirmed and suspected COVID-19 deaths in each province on Java Island up to 2nd September 2020 and 7th December 2020.

Province	Confirmed deaths		Suspected deaths	
	Up to 2 nd September	Up to 7 th December	Up to 2 nd September	Up to 7 th December
Jakarta	1,237	2,823	4,979	9,352
West Java	258	953	542	2,113
Central Java	1,037	2,464	2,569	6,197
Yogyakarta	42	154	101	460
East Java	2,423	4,616	3,872	7,407
Banten	111	360	191	677
Java Island	5,108	11,370	12,254	26,206

The transmission model was calibrated to the death data shown in **Figure 4.5** for all provinces on Java Island (the province-level calibrations are shown in **Figures S4.1** and **S4.2**). The first projections generated using the SARS-CoV-2 transmission model fitted up to 2nd September 2020 (**Figure S4.3**) data suggested that while R_t was well below that observed at the beginning of the epidemic, this was driven primarily by the impact of control measures rather than the accumulation of population-level immunity. As a result, in the absence of additional control measures, death rates were likely to rise for the remainder of the year in all provinces, pushing all provinces beyond available hospital capacity. Model simulations also suggest that the reimplementation of PSBB could largely prevent capacity from being exceeded but would not prevent a subsequent wave if such control was not maintained.

Subsequently, between the two sets of simulations (2nd September 2020 and 7th December 2020), both confirmed deaths and the inferred estimates of total suspected deaths increased from 5,108 to 11,370 and 12,254 to 26,206, respectively, across Java. At the island level, the estimated attack rates on both dates increased from 1.21% to 2.57% and 2.95% to 6.03% based on confirmed deaths and assuming all suspected deaths as COVID-19 deaths, respectively (**Figure 4.6A**). However, at the province level, estimates of attack rate and total burden from COVID-19 differ significantly, with Jakarta accumulating the highest attack rates in the region by 7th December 2020 (**Figure 4.6B**; **Table S4.2**). In all provinces and based on models fitted to either suspected or confirmed deaths, there were consistent increases of around 2-3 times on the province-level attack rate from 2nd September to 7th December 2020. However, as was seen at the island level, discrepancies between the estimated attack rates based on the model fitted to suspected deaths and confirmed deaths data were still observed at the province level, with the highest difference observed in Jakarta.

Projections of future scenarios from December 2020 (**Figure 4.6C**; and **Figure S4.4** for province-level breakdown), incorporating these changes in estimated attack rate and extrapolating current trends of R_c , leading to the projected daily incidence of mortality across the island continuing to grow throughout the first half of 2021 irrespective of whether reported or suspected mortality are more reflective of true direct COVID-19 mortality. In this scenario, with future $R_c = 1.25$, the epidemic would be projected to peak earliest in Jakarta, driven by the higher degree of population-level immunity implied by the higher cumulative attack rate on 7th December 2020. This peak's timing was sensitive to the mortality metric the model is calibrated to, with projected peaks occurring early in 2021 for a current scenario based upon suspected deaths and towards the end of the first quarter of 2021 based on reported deaths (**Figure 4.6C**; and **Figure S4.4**). Subsequently to these simulations, the incidence of COVID-19 deaths in Jakarta peaked in late January, prior to the roll-out of the vaccine to the elderly in the province (**Figure S4.5**), aligning more closely to the projections based upon these funeral

data than those based upon confirmed deaths alone. Jakarta has also seen the largest and most steady subsequent decline of all provinces in Java (**Figure S4.6**), supporting the modelling result that population-based immunity due to the mature stage of the epidemic is having the largest impact in this province. However, in all provinces, at no point in any of the simulation 'current' scenarios were there sufficient population immunity to preclude a subsequent upsurge in deaths if transmission levels returned to those estimated at the beginning of the pandemic ($R_c \approx 2.00$) prior to the completion of an effective vaccination campaign.

Figure 4.7 shows the potential values of COVID-19 mass vaccinations based on the three different future scenarios summarised in terms of the proportion of lives lost before 'return to normal' (**Figure 4.7A**) and the total remaining lives to be saved (deaths that can still be averted) after 'return to normal' (**Figure 4.7B**). Reimposing suppression scenarios in areas where epidemics are on an upwards trajectory would significantly reduce lives lost while the vaccine is rolled out. In some settings, such as Jakarta, assuming COVID-19 caused all suspected deaths, a combination of current control measures and increasing levels of population immunity may reduce transmission and burden to low levels temporarily. At this point, the future incremental impact of suppression measures would likely be limited. However, in such scenarios, I estimate that a high loss of life would occur in a subsequent lifting of control measures, highlighting the need for ongoing control measures and the substantial remaining incremental value of an effective vaccination campaign (**Figure 4.7B**).

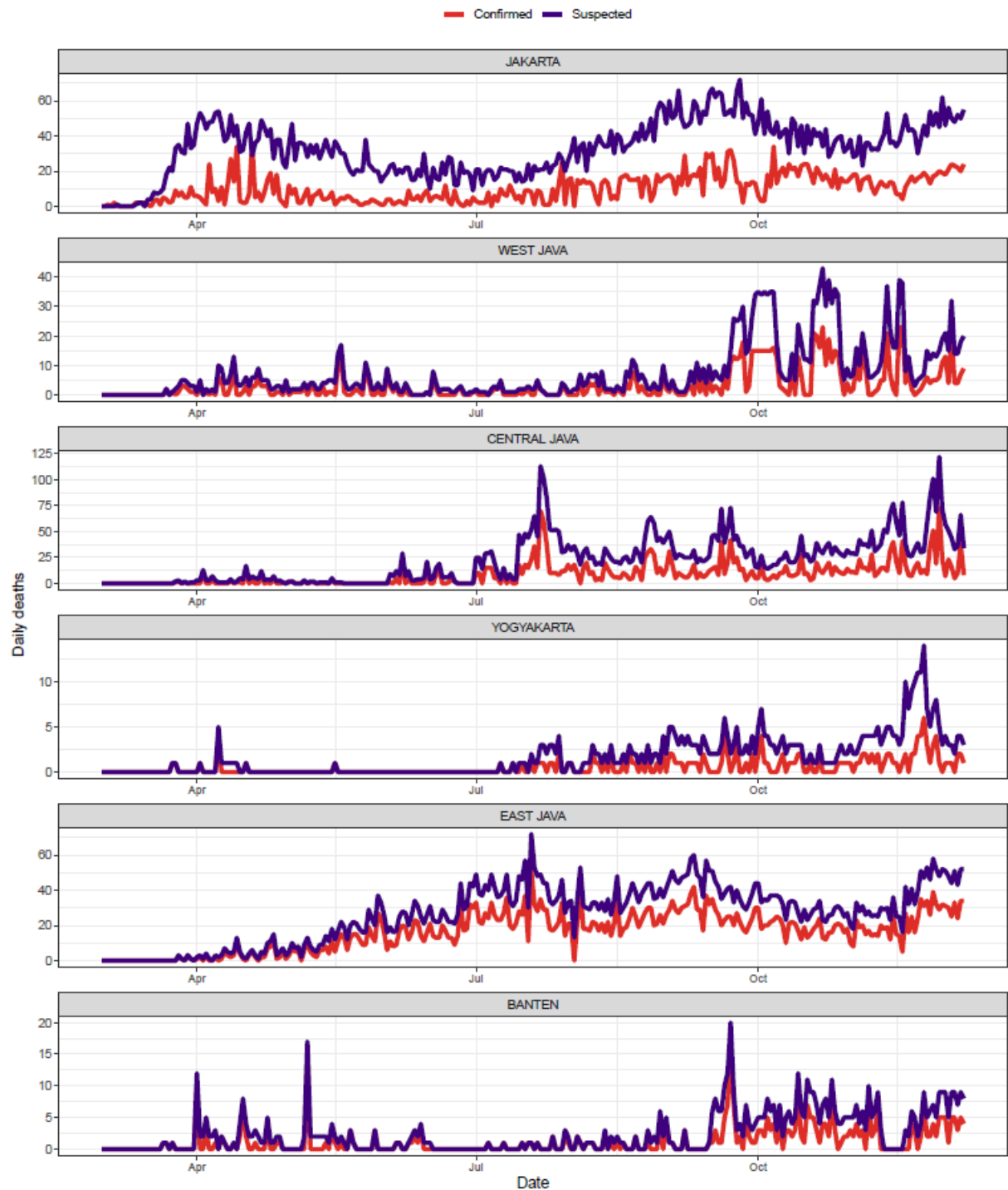


Figure 4.5. Confirmed and suspected COVID-19 death data for all provinces in Java Island. The suspected deaths in Jakarta were the reported C19P burials, while median estimates from probabilistic simulations were used for other provinces.

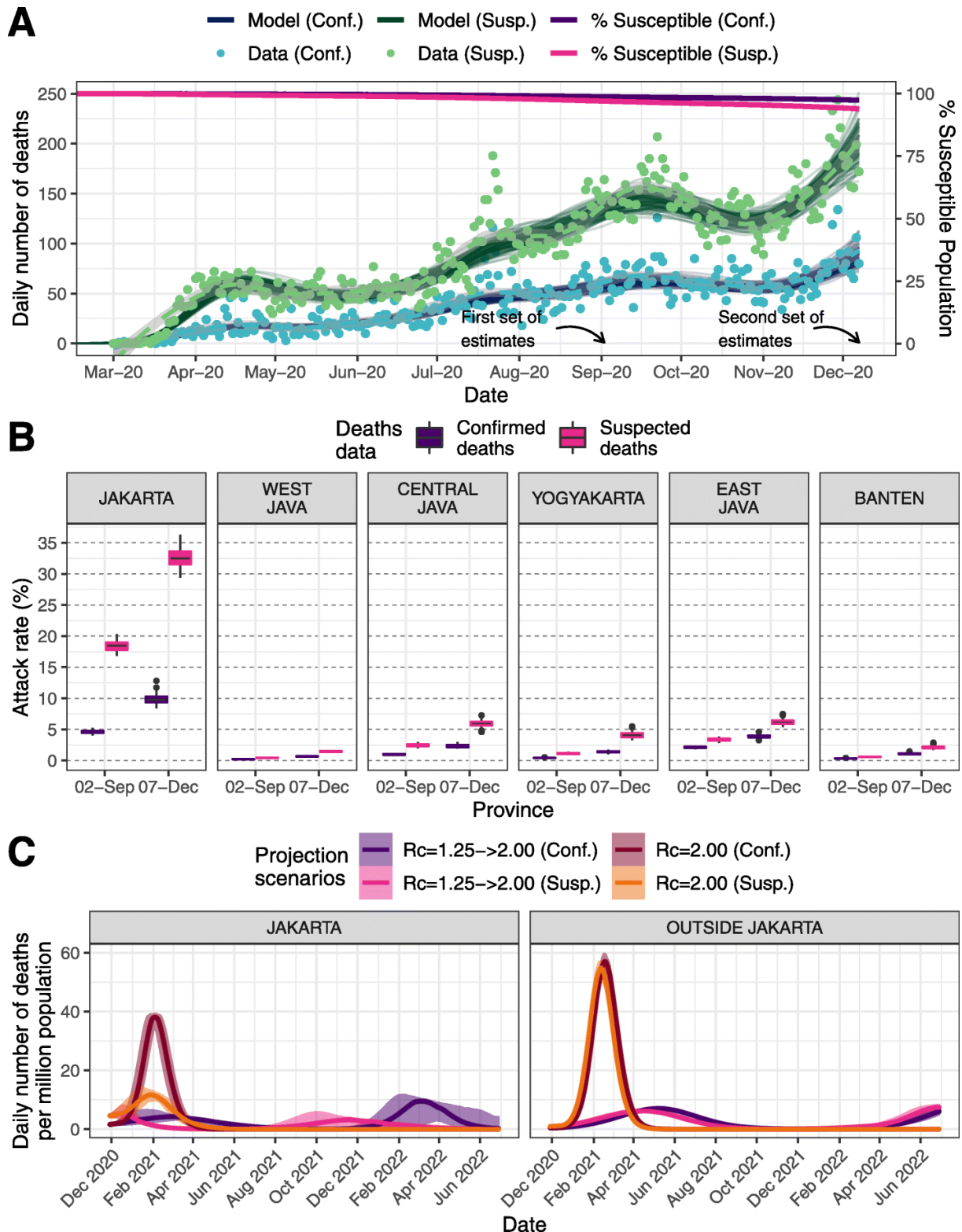


Figure 4.6. A) Model fitting to confirmed and suspected (both confirmed and probable) COVID-19-related deaths and inferred population susceptibility in Java; green and blue dots show data on reported and suspected, respectively (where suspected includes augmented estimate of probable deaths in provinces outside Jakarta), with associated median (lines) and 95% CrI (shaded areas) of model fits. B) Estimated province-level attack rates (cumulative proportion infected) based on confirmed (purple) and suspected (pink) COVID-19-related deaths. C) Projections of the daily number of deaths per million population due to COVID-19 based on four different transmission scenarios.

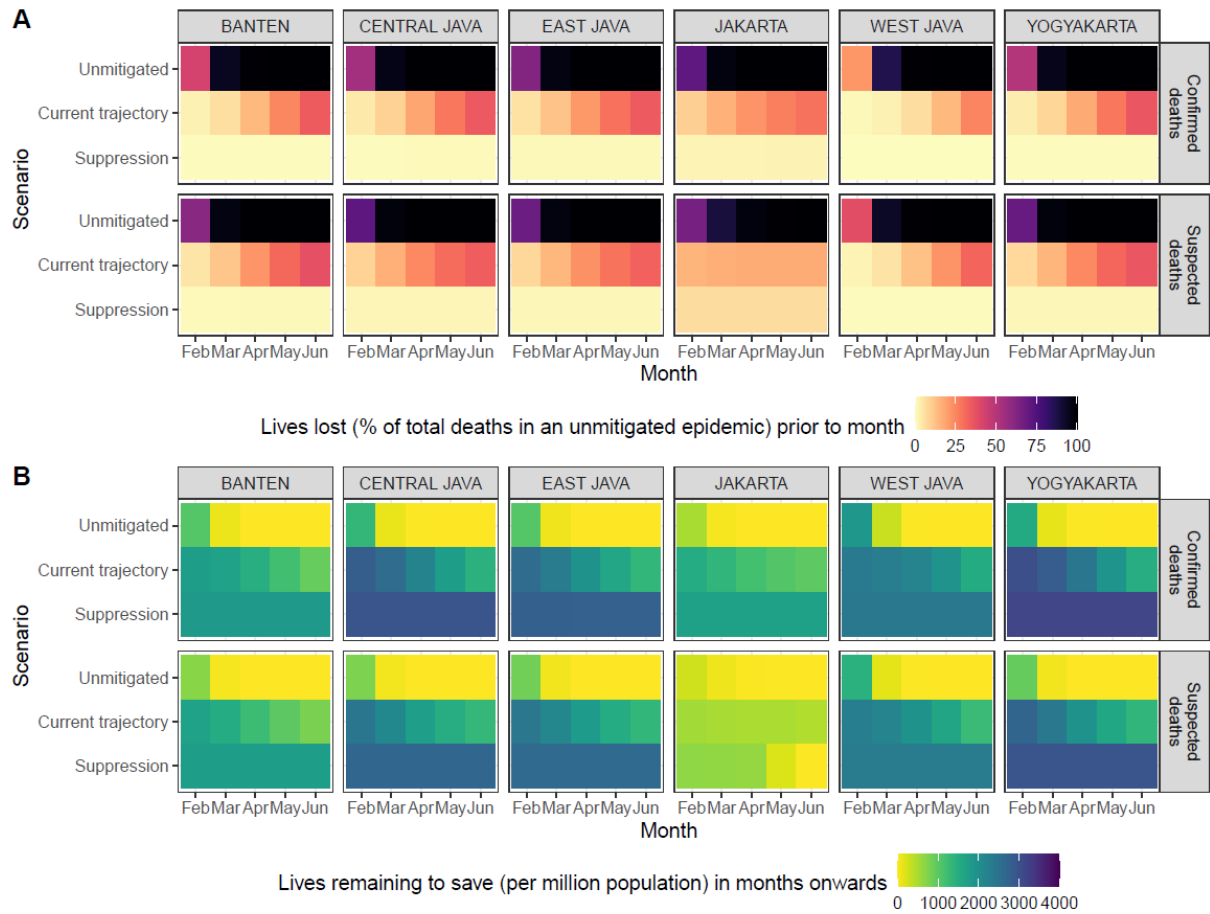


Figure 4.7. A) The projected percentage of lives lost (compared to total deaths from an unmitigated epidemic scenario) prior to the start of each month from February to June 2021, based on each simulation scenario and model fitted to confirmed or suspected deaths in each province in Java. B) Projected number of lives remaining to be saved (or deaths that can still be averted) per million population after the start of each month from February to June 2021, based on each simulation scenario and model fitted to confirmed or suspected deaths in each province in Java.

4.4 Discussions

The results presented in this chapter demonstrate how estimates of the level of infections in the population (attack rates) based on a transmission model of SARS-CoV-2 can vary depending on the data used for the model calibration process. In this chapter, I compared the results from calibrating the model to confirmed COVID-19 deaths and suspected COVID-19 deaths, which include both confirmed and probable COVID-19 deaths. The findings reveal that the attack rate estimates from models calibrated to suspected deaths data could be 2-3 times higher than estimates accounting only for confirmed deaths. Consequently, future scenario simulations from such models were affected by differences in the baseline estimates of population immunity. I estimated that this could greatly affect the future trajectory of the virus in the population regarding how much NPI restrictions should be implemented, especially in the province with a high discrepancy between confirmed and suspected deaths data, such as Jakarta. In the context of COVID-19 vaccination rollouts that were under preparation at that time, the differences in the intensity of restrictions and, additionally, the population adherence

to such restrictions could translate to how many lives could be saved by the vaccination program in the future had already gone due the infections by the SARS-CoV-2 virus.

Better quantifying impact in the past helps us to better understand likely scenarios in the future. In September 2020, the first set of projections suggested that C19P funeral data could indicate up to a four-fold increase in cumulative exposure to the virus relative to confirmed deaths. However, even when assuming a higher disease burden in the population, immunity accumulated at the population level would not prevent the burden from increasing throughout the remainder of 2020. The model output also suggested that measures to suppress the virus could prevent such a scenario but would need to be sustained to prevent further upsurges. From early 2021, these projections appear to have been valid as transmission declined in Jakarta whilst PSBB was implemented between 14th September – 11th October 2020 but subsequently resurged once restrictions were lifted. At the beginning of 2021, Java's epidemiological situation is substantially worse than in September, with record deaths reported week-on-week (Ratcliffe & Cahya, 2021). Subsequently, the model projections, based upon C19P funeral data, of a likely decline in the epidemic in Jakarta independent from any vaccine impact has also come to fruition, again highlighting the utility of understanding the true impact of the disease in the population using syndromic measures of mortality.

After the completion of this study, several seroprevalence survey studies in Java were published. Herlinda et al. and Ariawan et al. published seroprevalence estimates of 28.52% and 44.5% for studies conducted between November 2020-February 2021 and March 2021, respectively (Ariawan et al., 2022; Herlinda et al., 2021). These estimates are closer to the modelled estimate of the attack rate based on suspected deaths data in Jakarta (32.48%, 95% CrI 30.09-34.63%) than the one from confirmed deaths data only (18.43%, 95% CrI 17.04-19.66%) in early December 2020. In two districts in East Java, Megasari et al. estimated an overall COVID-19 seroprevalence of 11.4% from a survey conducted between June to December 2020 (Megasari et al., 2021), also closer to the estimate based on suspected deaths (6.17%, 95% CrI 5.46-7.38%) than confirmed deaths (3.85%, 95% CrI 3.39-4.40%). In Yogyakarta, Ahmad et al. reported a seroprevalence rate of 31% from a study conducted between March and April 2021, a much larger number compared to the estimated attack rates at the end of 2020, which may reflect a rise in infections following the surge of the Alpha variant in early 2021 (Ahmad et al., 2023). Despite the quantitative differences between the modelled estimates and the empirical measures of population exposure to the virus, which may be due to the variability of district-level population exposure within each province, these more recently published data showed how modelled estimates based on confirmed death data only might well underestimate the 'true' disease burden in the population.

Despite the qualitative validity of both the September and December 2020 projections, there are multiple limitations associated with these analyses that should be noted, particularly as the estimates of attack rates in all provinces in Java have increased substantially. Firstly, it remains difficult to say what level of population immunity is required to achieve herd immunity as individual immune responses to the virus are still not yet well understood (including their strength and duration) (Altmann et al., 2020; Stephens & McElrath, 2020), and heterogeneity in population mixing beyond age-structure likely play important roles (Aschwanden, 2020; Britton et al., 2020). Moreover, the estimates of counterfactual 'return-to-normal' scenarios rely upon an estimate of $R_c = 2.00$ from the early stage of the epidemic in Jakarta, a period in which data were particularly limited and, given increasing global concern around the pandemic, where a degree of behaviour change relevant may have already occurred. This estimate is also below those estimated in the early stage of the epidemic from other settings (Flaxman et al., 2020b), which may represent a conservative measure of the basic reproduction number. These limitations around the inherent transmissibility and critical immunity threshold to control the virus need to be further considered in light of recent concerns of new variants of concern across the globe that appear more transmissible (Meldrum & Magome, 2021; Sabino et al., 2021; Volz et al., 2021). Factors such as the potential for reinfection and variations in the strength and duration of immunity following infection or vaccination further complicate this determination (Aschwanden, 2021; Morens et al., 2022). There have also been observed resurgences in populations where attack rates had likely passed many estimates of the herd immunity threshold (Buss et al., 2021; Sabino et al., 2021; Sharma et al., 2021). As our knowledge of these complexities continues to develop, it will likely shape our perspective on what achieving herd immunity for COVID-19 entails and inform our approach to managing future resurgences and epidemics of cases.

The initiation of the vaccination campaign in the middle of January (Jiao & Aditya, 2021a) provides hopes for more sustainable control of the virus. However, challenges in access and distribution (J. H. Kim et al., 2021) and uncertainty in vaccine efficacy (J. H. Kim et al., 2021) could hamper the life-saving impact of the vaccination program. In addition, possible introductions of variants of concern (VOC) that can escape immune response (Kupferschmidt, 2021), exhibit increased transmissibility (Davies, Abbott, et al., 2021; Faria et al., 2021), or cause more severe disease (New and Emerging Respiratory Virus Threats Advisory Group (NERVTAG), 2021) could also pose additional challenges in controlling the spread of the virus. Those changes in virus characteristics could lower the real-life vaccine effectiveness, increase the threshold to reach 'herd immunity', and threaten the healthcare capacity once again if infections from those VOC were able to dominate and spread rapidly. Up to early 2021, Indonesia had reported several VOC (i.e., B.1.1.7 (Widianto, 2021a), B.1.525 (Panama & Katriana, 2021), and a variant with E484K mutation (Reuters staff, 2021)) via a ramp-up of

genomic surveillance capacity at the turn of the year (Rochmyaningsih, 2021). Whilst the sporadic nature of the genomic samples makes it difficult to determine whether local transmission had been established or not (Rochmyaningsih, 2021), such VOCs further underline the need to maintain control whilst the vaccination campaign is ongoing.

Despite the unprecedented speed of global vaccine development, this study indicates that in the absence of NPIs implemented over the previous year, this campaign would have been too late to prevent most deaths that at that time remained avertable. It also highlights the ongoing value and needs to maintain control measures implemented at that time as the vaccine was being rolled out. Given low estimated attack rates and increasing trends in transmission across much of the island at that time, the analysis results suggest that further measures aimed towards suppression of the disease over the upcoming months would substantially increase the proportion of the population who receive the vaccine prior to being exposed to infection, leading to a likely substantial incremental impact of the vaccination campaign. However, the analysis did not account for the socio-economic costs of such approaches, which would need to be factored into balanced decision-making.

The case for maintaining or increasing control measures is likely more intuitive to grasp when the incidence of cases and deaths continues to rise. However, the transmission model projections for Jakarta, particularly those incorporating suspected deaths, suggest that population-level immunity contributes largely to the decline in observed deaths. This effect may have consequences for the perceptions of both the vaccine's relative impact, with deaths declining at a faster rate in Jakarta relative to other provinces as the vaccine was being rolled out, as well as the ongoing need for NPIs and/or high vaccine uptake. In such circumstances, the counterfactual scenario of a 'return-to-normal', which produces major upsurges in cases and deaths in every province regardless of mortality metric, provides a valuable reminder that the epidemic, and the need to control it, was far from over in any region of Java.

4.5 Conclusions

This chapter provides further evidence of the value of syndrome-based mortality as a metric, which is less dependent upon the testing capacity to estimate transmission trends and evaluate intervention impact. Further relaxation of measures would lead to more rapidly progressing epidemics, depleting the eventual incremental effectiveness of the vaccine. Maintaining adherence to control measures in Jakarta may be particularly challenging if the epidemic enters a decline phase, but it will remain necessary to prevent a subsequent large wave. Elsewhere, higher levels of control with NPIs are likely to yield a high synergistic vaccine impact. Enduring vigilance is vital whilst the vaccination campaign is rolled out, especially in light of the emergence of VOC across the globe.

Chapter 5: A decade of malaria control in Indonesia (2010-2019): analysis of routine surveillance data

In the next three chapters (**Chapters 5, 6, and 7**), the analyses shift its focus from COVID-19 to malaria, a disease that is still endemic in some parts of Indonesia despite more than a century of ongoing efforts to eliminate local transmission (I. R. F. Elyazar et al., 2011; Takken et al., 1991). Due to continuous efforts to eliminate the disease and the natural diversity of the country, the landscape of malaria across Indonesia is very heterogeneous. In this chapter, the analysis focused on characterising malaria dynamics at the national and regional levels. To facilitate the analysis, the country was divided into seven malaria transmission zones, each representing one of Indonesia's seven main islands: Sumatra, Java and Bali, Kalimantan, Sulawesi, Nusa Tenggara, Maluku, and Papua. Using routinely collected malaria surveillance data, I used multiple malaria metrics generated from the surveillance system to trace the progress toward malaria elimination at the national level and in each region. The 2010-2019 period is particularly intriguing as it marks a decade since the Indonesian government's pledge to eliminate local transmission in the country by 2030.

5.1 Introductions

5.1.1 Background

Designing optimal control strategies for malaria is challenging due to the heterogeneity of epidemiological factors related to the disease in Indonesia. Those factors include the heterogeneous landscape of endemicity, differences in population densities ranging from major cities to highly rural areas, multiple malaria vectors with different behaviours and bionomics, two co-endemic and dominant malaria species (*Plasmodium falciparum* and *Plasmodium vivax*), and increasing concerns around zoonotic malaria (*Plasmodium knowlesi*) infections (I. R. F. Elyazar et al., 2011, 2013). Additionally, controlling malaria in mobile and migrant populations (MMPs) presents significant challenges, particularly in areas approaching elimination (Ekawati et al., 2020).

Despite these challenges, Indonesia's malaria control and elimination programs from 2010-2019 have made substantial progress in the country's fight to eliminate malaria. In 2017, Indonesia achieved a major milestone of declaring more than half of the districts across the country (accounting for around 72% of the country's population) malaria-free (reporting no local malaria transmission in three consecutive years) (Sitohang et al., 2018). The achievement is thought to be largely attributable to the intensification of malaria control efforts since the early 2000s, followed by a passing of a National Ministerial Decree on Malaria Elimination in 2009. The latter gave decentralised authorities (up to the district level) the ability and political

commitment to implement effective and locally-tailored malaria control programs. The Ministerial Decree also kicked off massive improvements in many aspects of malaria control programs such as financing, scale-up of artemisinin combination therapy (ACT) and mass distributions of long-lasting pyrethroid-insecticide treated nets (LLINs), mandated laboratory confirmations, diagnosis quality assurance, screening and treatment in pregnant women, and improved surveillance and reporting (**Figure S5.1**). Therefore, objective and quantitative measurement of the role of these endeavours in driving improvements in control is needed to ensure that future control and elimination efforts will be deployed effectively and efficiently.

Malaria routine surveillance data have been increasingly used to define national and regional-level targets, estimate disease burden, and measure the impact of control strategies (Alegana et al., 2020). In Indonesia, surveillance and reporting of malaria cases have considerably improved from only covering 26-50% of districts at the beginning of 2010 to more than 75% in 2015 (Sitohang et al., 2018). However, given the scale-up in testing capacity and changes in reporting behaviour, temporal patterns of reported malaria cases from surveillance data can prove difficult to interpret. For instance, more (and more accurate) testing may coincide with the detection of more cases, which may not reflect an actual increase in burden.

In this chapter, I analysed a decade of routine malaria surveillance data from across Indonesia to better understand recent progress in malaria control. The analysis included characterisations of the overall trends of malaria surveillance metrics, i.e., case counts and test positivity ratios (TPR). Motivated by the potential limitation of this data, as described before, I also looked at trends of malaria case profiles (e.g., proportions of cases by parasite species, age, and sex) and compared them with patterns that we would normally expect to see as we move toward malaria elimination. For example, controlling and eliminating *P. vivax* have been thought to be more difficult than *P. falciparum*. Thus, it is expected to be the dominant malaria species as countries are heading towards elimination (Cotter et al., 2013; Howes et al., 2016), as we have also seen in several countries in the Latin Americas (Ferreira & Castro, 2019). Furthermore, the average age of infections is expected to increase when malaria transmission intensity is reduced due to the waning of immunity in adults (Griffin et al., 2014). Finally, we may expect the infections to become more frequent in males, especially if infections become more occupational-driven (Cotter et al., 2013; Sandfort et al., 2020). By collectively considering multiple metrics derived from the routine surveillance data, it may be possible to uncover trends in the ‘true’ burden of malaria infections in Indonesia to guide decision-making.

5.1.2 Aims

Using the routine surveillance data collected by the National Malaria Control Program (NMCP) during the period, I aimed to:

1. Describe the heterogeneous malaria epidemiology across the country.
2. Explore the changes in trends of various malaria metrics that occurred throughout 2010-2019.
3. Explore correlations and relationships between those malaria metrics to better measure progress toward malaria elimination.

5.2 Data and methods

5.2.1 Data

5.2.1.1 Malaria case data

Monthly aggregated district-level malaria routine surveillance data were obtained from the National Malaria Control Program (NMCP) of the Ministry of Health (MoH) of the Republic of Indonesia from 2010 to 2019. For this study, monthly malaria cases and test data were used. Details on variables in the data used for the analysis and their descriptions are listed in **Table S5.1**. **Figures 5.1A** and **5.1B** show the number of months from January 2010 until December 2019 that at least a single malaria test or a single malaria case was reported at the district level.

5.2.1.2 Population data

District-level population data were obtained from the 2010 and 2020 census results by Statistics Indonesia (Badan Pusat Statistik, 2021, 2011). The population data comprise the total population by 5-year age group, from 0-5 years old to over 75 years old age group. Population numbers by region based on the 2020 census are shown in **Table S5.2**.

5.2.2 Methods

5.2.2.1 Between-census population interpolations

Simple linear regression models were used to interpolate the yearly district-level population counts for each age group in 2011-2019, based on the population data obtained from the 2010 and 2020 Census. An evaluation of the usage of linear interpolations between two censuses in the United States of America has shown that for demographic characteristics, the interpolations performed well at the county level (Weden et al., 2015).

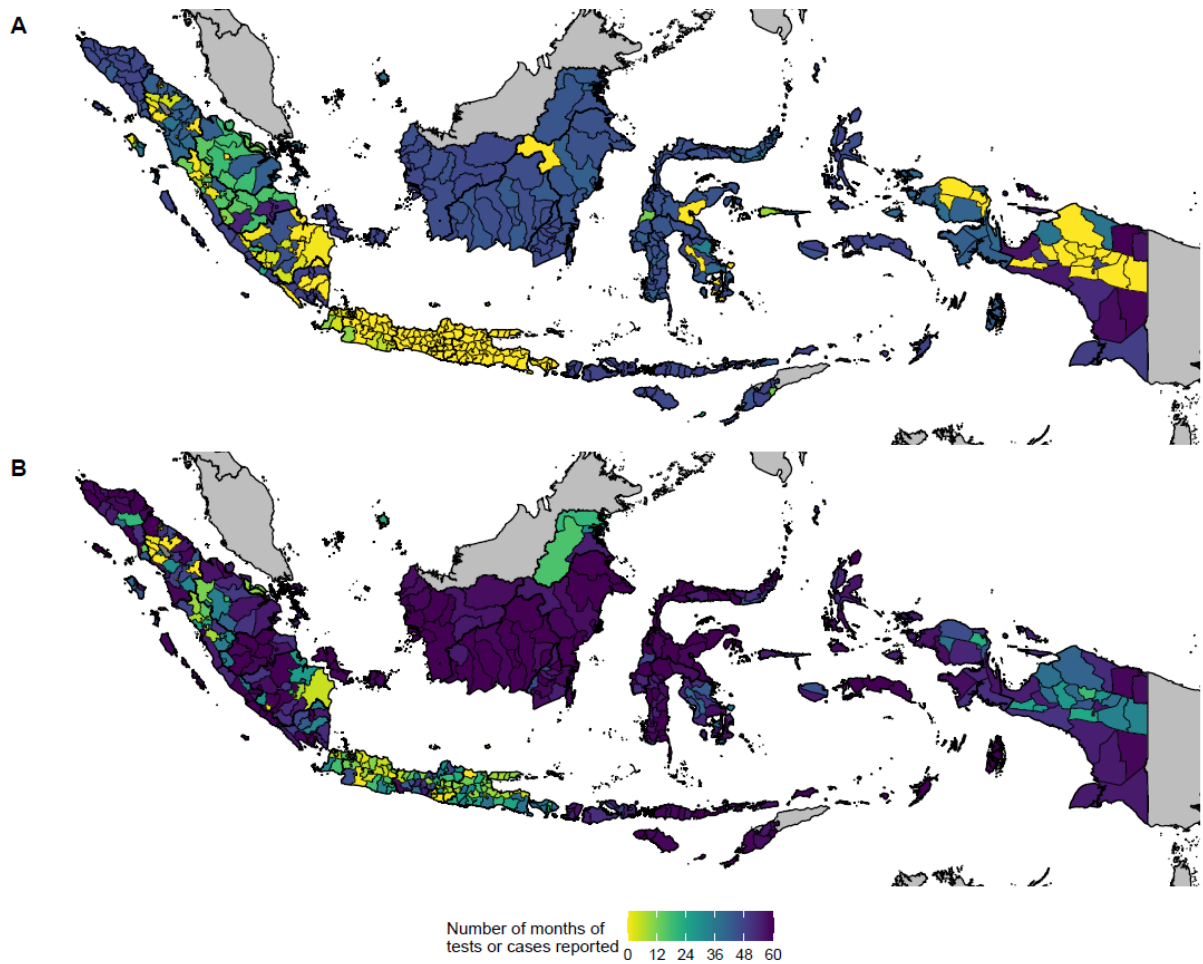


Figure 5.1. Number of months that at least a single malaria test or a single malaria case was reported in a district. A) Between January 2010 - December 2014; and B) Between January 2015 - December 2019.

5.2.2.2 Estimating trends of malaria metrics using Generalised Additive Model (GAM)

Here, I used Generalised Additive Models (GAM) to produce estimates of overall regional trends allowing for imperfect reporting at the district level throughout 2010-2019. These models allow complex non-linear trends to be captured by allowing the relationships between the covariates and the response variable to be described by smooth functions or splines (Pedersen et al., 2019; Simpson, 2018). The models were fitted independently for each region, with district and month-year as a categorical factor covariate and a penalised smoothing spline covariate, respectively.

GAM with a negative binomial family and population counts as the model offset variable were used to model cases and tests per 1,000 population ([Equation 5.1](#)). Negative binomial distribution was chosen to account for overdispersion in the distributions of cases and tests. Additionally, cases and tests were also modelled with GAM with a Poisson family distribution and presented in the **Appendix** as comparisons. GAM with a binomial family and logistic link function was used to model the metrics and case profiles measured as proportions (Eq. 5.2).

The `mgcv` package in R (Wood, 2021) was used for the implementation of GAM (Wieling, 2018; Wood, 2003, 2011).

Equation 5.1:

$$Y_{i,t} \sim NB(N_{i,t}\lambda_{i,t}, r)$$

$$\log[E(Y_{i,t})] = \beta_0 + \beta_{1i}X_{1i} + \log(N_{i,t}) + g(X_{2i,t})$$

with $Y_{i,t}$ as either the number of cases or tests in district i at time (month-year) t , $N_{i,t}$ as the population counts in district i at time t , $\lambda_{i,t}$ as the case or test rate per population in district i at time t , r as the overdispersion parameter of the Negative Binomial (NB) distribution, β_0 as the model intercept, β_{1i} as the regression parameter for varying district-level intercepts, X_{1i} as the dummy variable for the district categorical covariate, and $g(X_{2i,t})$ as the spline function for the time covariate $X_{2i,t}$.

Equation 5.2:

$$Y_{i,t} \sim Binomial(n_{i,t}, \pi_{i,t})$$

$$\log\left(\frac{\pi_{i,t}}{1 - \pi_{i,t}}\right) = \beta_0 + \beta_{1i}X_{1i} + g(X_{2i,t})$$

with $Y_{i,t}$ as the number of cases in a specific population group (males or over 14 years old) or infections identified with a specific parasite species (*P. vivax*) in district i at time (month-year) t , $n_{i,t}$ as the total reported malaria cases in district i at time t , and $\pi_{i,t}$ as the proportion of malaria cases in a specific population group (males or over 14 years old) or infections identified with a specific parasite species (*P. vivax*) in district i at time t . When modelling TPR, $Y_{i,t}$ is the number of reported malaria cases and $n_{i,t}$ is the number of malaria tests reported.

The metrics and case profiles modelled, and their respective distribution families are shown in **Table 5.1**. The intercept for the regional-level trend lines was approximated using the median of estimated intercepts of all districts within a region.

Table 5.1. The metrics and cases profiles modelled and their distribution families.

Metrics and case profiles	Distribution family
Cases per 1,000 population (overall and by age groups)	Negative binomial
Tests per 1,000 population	Negative binomial
Test positivity ratio (TPR, %)	Binomial (logit)
Proportion of <i>P. vivax</i> cases (%)	Binomial (logit)

Proportion of cases in males (%)	Binomial (logit)
Proportion of cases in over 14 years old (%)	Binomial (logit)

5.2.2.3 Characterising the relationship between age of infections and malaria incidence using Generalised Linear Model (GLM)

In the previous section, the relationship between the age of infections (i.e., the proportion of cases in adults) and malaria endemicity was measured indirectly by comparing trends over time of both metrics. In this section, I developed a framework that summarises all age-specific data, analysing the relationship between transmission and age to see whether consistent patterns were observed across Indonesia. The relationship between the mean age of infections (μ) and the Annual Parasite Incidence per 1,000 population (API per 1,000) was assumed to be exponential as an approximation to the acquisition of clinical immunity to malaria in older age groups in the high transmission area (Kleinschmidt & Sharp, 2001). The relationship was modelled with an exponential function with three parameters (b_1 , b_2 , and b_3):

$$\mu = b_1 e^{b_2 \log(API)} + b_3$$

The age of infections with mean μ was assumed to be distributed under the Gamma distribution (a flexible and positive definite distribution) function with a shape parameter (α) and an inverse scale (or rate) parameter (β). Summing up parameters $b_1 + b_3$ is the average age in the limit towards API per 1,000 = 0 (i.e., elimination). Parameter b_3 represents the extent to which that average age is independent of transmission. The remainder (b_1) scaled to the power of $\log(API)$ using an e^{b_2} parameterisation, which allows equal prior weight on an increasing or decreasing relationship with transmission.

We assumed the standard deviation (σ) of the distribution to be a constant (but estimated within the model). The relationship between μ and σ of the Gamma distribution and their parameters, α and β , are described as follows:

$$\alpha = \mu^2 / \sigma^2$$

$$\beta = \mu / \sigma^2$$

The cumulative density of the Gamma distribution of age of infections was then used to calculate the set of probability π , which is a vector representing proportions of malaria cases in 0-4 (π_1), 5-9 (π_2), 10-14 (π_3), and over 14 years old (π_4) age brackets:

$$\pi_1 = \int_0^5 \frac{\beta^\alpha}{\text{Gamma}(\alpha)} y^{\alpha-1} e^{-\beta y}, \pi_2 = \int_5^{10} \frac{\beta^\alpha}{\text{Gamma}(\alpha)} y^{\alpha-1} e^{-\beta y},$$

$$\pi_3 = \int_{10}^{15} \frac{\beta^\alpha}{\text{Gamma}(\alpha)} y^{\alpha-1} e^{-\beta y}, \pi_4 = \int_{15}^{\infty} \frac{\beta^\alpha}{\text{Gamma}(\alpha)} y^{\alpha-1} e^{-\beta y}$$

The reported number in each age brackets of 0-4, 5-9, 10-14, and ≥ 15 years old are represented by Y_1, Y_2, Y_3 , and Y_4 , respectively, where $Y_i \sim \text{Poisson}(\lambda_i)$. Hence, the total number of cases for all age groups is $n \sim \text{Poisson}(\lambda_1 + \lambda_2 + \lambda_3 + \lambda_4)$. The multinomial distribution for $Y = (Y_1, Y_2, Y_3, Y_4)$ given n (and given $\pi_j = \frac{\lambda_j}{\sum_{i=1}^k \lambda_i}$) is defined as:

$$Y \sim \text{Multinomial}(n, \pi).$$

With priors for other parameters:

$$b_1 \sim \text{Normal}(0, 10)$$

$$b_2 \sim \text{Normal}(0, 1)$$

$$b_3 \sim \text{Normal}(0, 10)$$

$$\sigma \sim \text{Gamma}(1.5, 0.1)$$

The model fitting process was done in a Bayesian framework by implementing the `rstan` package in R (Stan Development Team, 2020). Each year's district-level malaria case data were used for the model fitting process, filtering only observations with at least 30 malaria cases reported to reduce the noise from the low-level malaria case counts.

5.2.2.4 Measuring correlations between incidence and test positivity ratio

Malaria incidence per 1,000 population and TPR are some of the metrics for measuring changes in malaria transmission intensity that can be derived from routine surveillance data (Tusting et al., 2014). Roughly, TPR can be defined as:

$$TPR = \frac{MF}{(NMF + MF)}$$

where MF is the malaria fever rate in the population and NMF is the non-malaria fever rate in the population. Through that relationship, when MF is small (means also when malaria incidence is low), then we would expect a linear relationship between malaria incidence per 1,000 population and TPR. However, when MF is high, we would expect the relationship would be less linear. Hence, to measure the relationship between these two metrics, I calculated Spearman's rank correlation coefficient, a nonparametric method to measure the statistical dependence between the rankings of two variables. The correlations were measured by region, using monthly and yearly district-level observations. For the yearly data, correlations were also calculated after including only observations with the annual blood examination rate (ABER) of more than 5%. ABER represents the proportion of the population tested for malaria each year, where high values usually mean adequate surveillance efforts.

5.3 Results

5.3.1 Geographical heterogeneity of malaria transmission

A simple summary of the data shows that from 2010 to 2019, the number of reported malaria cases at the national level in Indonesia was reduced by half. Meanwhile, malaria tests, which reflect surveillance efforts, almost doubled within the same period (**Figure 5.2A**). Nationwide, *P. falciparum* cases have been reported more frequently than *P. vivax* cases throughout the decade (**Figure 5.2B**). Malaria cases were also found more frequently in males (**Figure 5.2C**) and in the over 15 years old population (**Figure 5.2D**). However, on a per 1,000 population basis, the number of malaria cases in children under 5 was the highest relative to other age groups (**Table S5.3**).

The geographical heterogeneity of malaria transmission in Indonesia is shown in **Figure 5.3**. In 2010, districts with API per 1,000 > 5 (categorised as high endemic) were found in all regions except Java and Bali, where malaria transmission and endemicity were comparatively low. Papua, the region reporting the highest burden of malaria in the country, has seen declines in malaria endemicity in some of its districts over the past decade. These declines mostly came from the districts of the West Papua province. In the Papua province, malaria endemicity declined in 2015 before rising to a higher level in 2019. Regions with high-endemic districts at the beginning of the decade, such as Kalimantan, Sulawesi, and Nusa Tenggara, managed to reduce the overall endemicity of the region, leaving some pockets of high-endemic malaria districts in 2019. In the Sumatra region, pockets of malaria transmission have been reduced, leaving districts with low endemicity heading toward malaria elimination. In Java and Bali, only one district reported API per 1,000 > 1 in 2019.

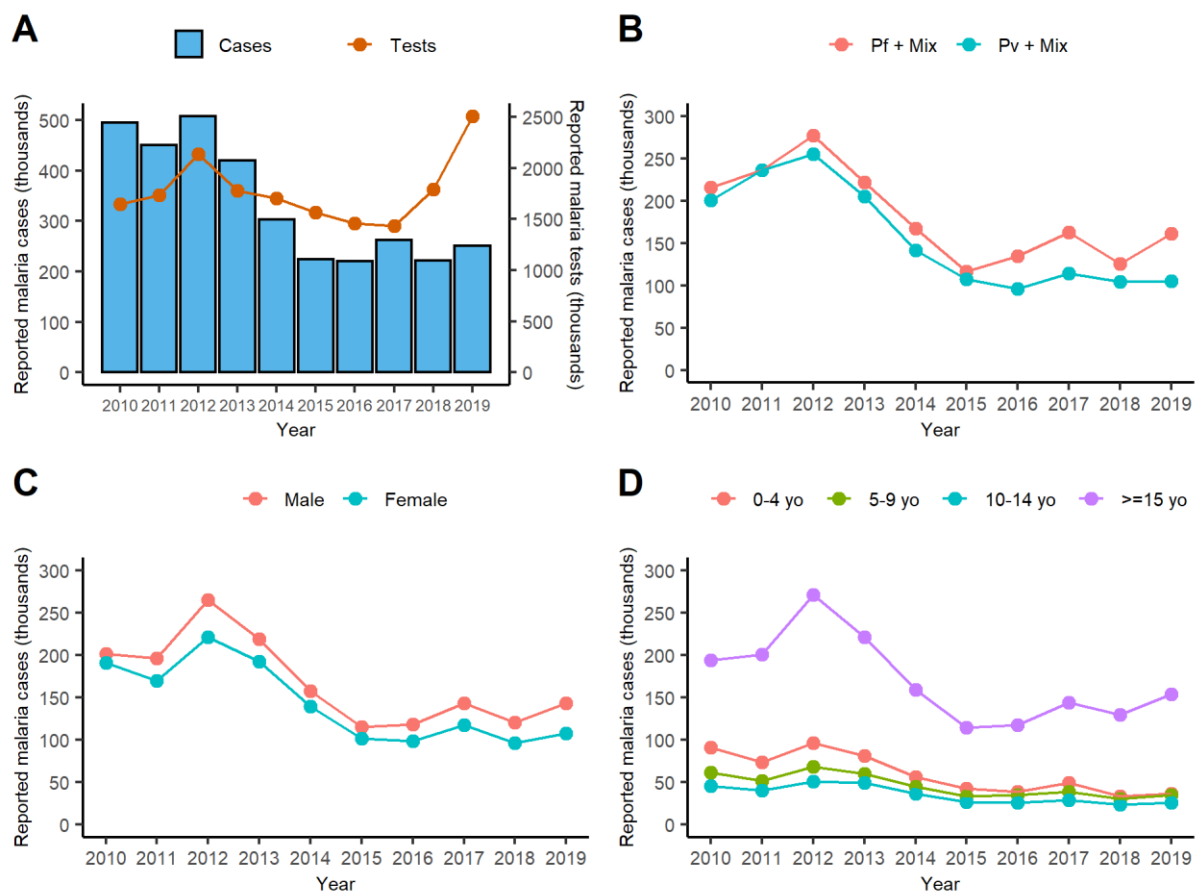


Figure 5.2. Yearly, national-level data of: A) malaria cases and tests; B) malaria cases by parasite species; C) malaria cases by sex; and D) malaria cases by age groups. Before 2015, some of the districts only reported yearly total malaria cases without further breakdowns by age, sex, or parasite species.

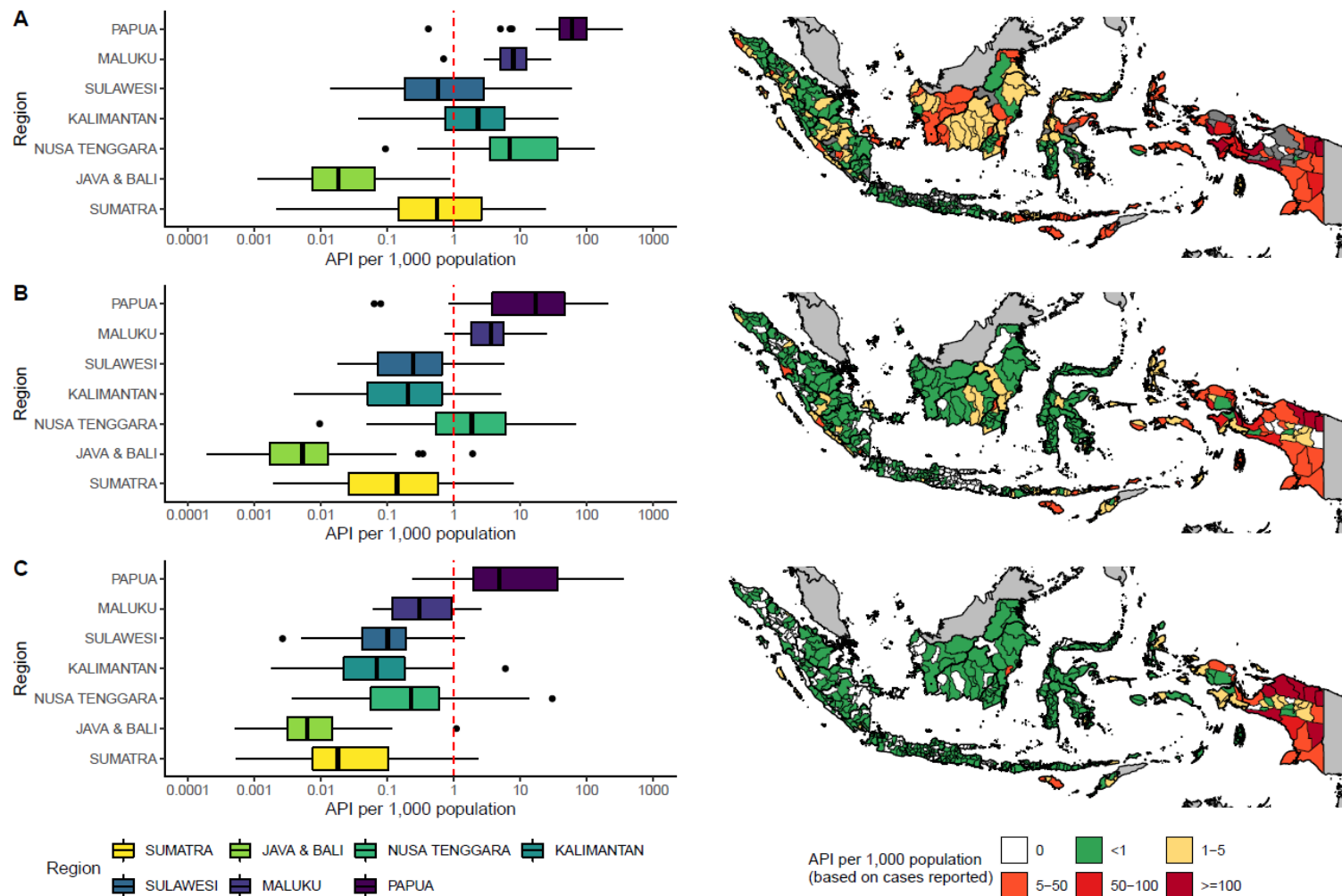


Figure 5.3. Boxplots of distributions of district-level API per 1,000 by region (based on reported malaria cases; left-hand side) and maps showing geographical heterogeneity of malaria endemicity in the country. Vertical lines of the boxplots represent 25th, 50th, and 75th percentiles, respectively. A) Based on reported data in 2010; B) 2015; and C) 2019. Dark greys denote areas not submitting routine malaria data.

5.3.2 Estimating trends of malaria metrics and malaria case profiles

Over the 2010–2019 decade, malaria incidence declined in all regions of the country, as estimated by GAM (**Figure 5.4A**). However, in some regions (Kalimantan, Sulawesi, and Papua), the declining trends slowed in the later years of the decade. The magnitude of the decline varied across regions, with the highest reduction estimated in the Sumatra region (69.5-fold) and the lowest in the Papua region (3.6-fold). The differences in magnitudes were likely influenced by the baseline malaria endemicity and the interventions implemented in each region. When examining the decline in malaria cases per 1,000 by age group (**Figure S5.2**), the magnitude of declines in malaria cases varied within each region for each age group. The largest declines occurred in younger populations (under 15 years old), especially in the youngest age group. These declines in malaria cases per 1,000 were estimated despite an increasing effort of case findings in the populations in almost all regions except Nusa Tenggara (**Figure 5.4B**). However, the testing efforts trends were estimated on a per 1,000 population basis. In absolute terms, as the population grew over the years, the testing efforts in Nusa Tenggara increased from 515 thousand tests in 2010 to 670 thousand tests in 2019. The substantial reduction in malaria burden across all Indonesian regions is also supported by the estimated test positivity ratio (TPR) trends, which also show declines across all regions (**Figure 5.4C**). However, in Papua, an increase in the modelled TPR pattern was observed in 2017 before declining again afterwards.

When focusing on ‘who’ is being infected and by ‘which species’ (**Figure 5.5**), cases are generally found in older patients, providing strong additional evidence of progress towards elimination. Furthermore, malaria cases have become increasingly male-dominant, which could indicate a shift towards a higher proportion of occupational exposure. However, there is no sign that *P. vivax* is becoming the dominating species in any region, despite some regions experiencing a slight shift in species distribution. Notably, Nusa Tenggara is the only region where there has been a consistent decline in the proportion of *P. vivax* infections in the last years of the decade.

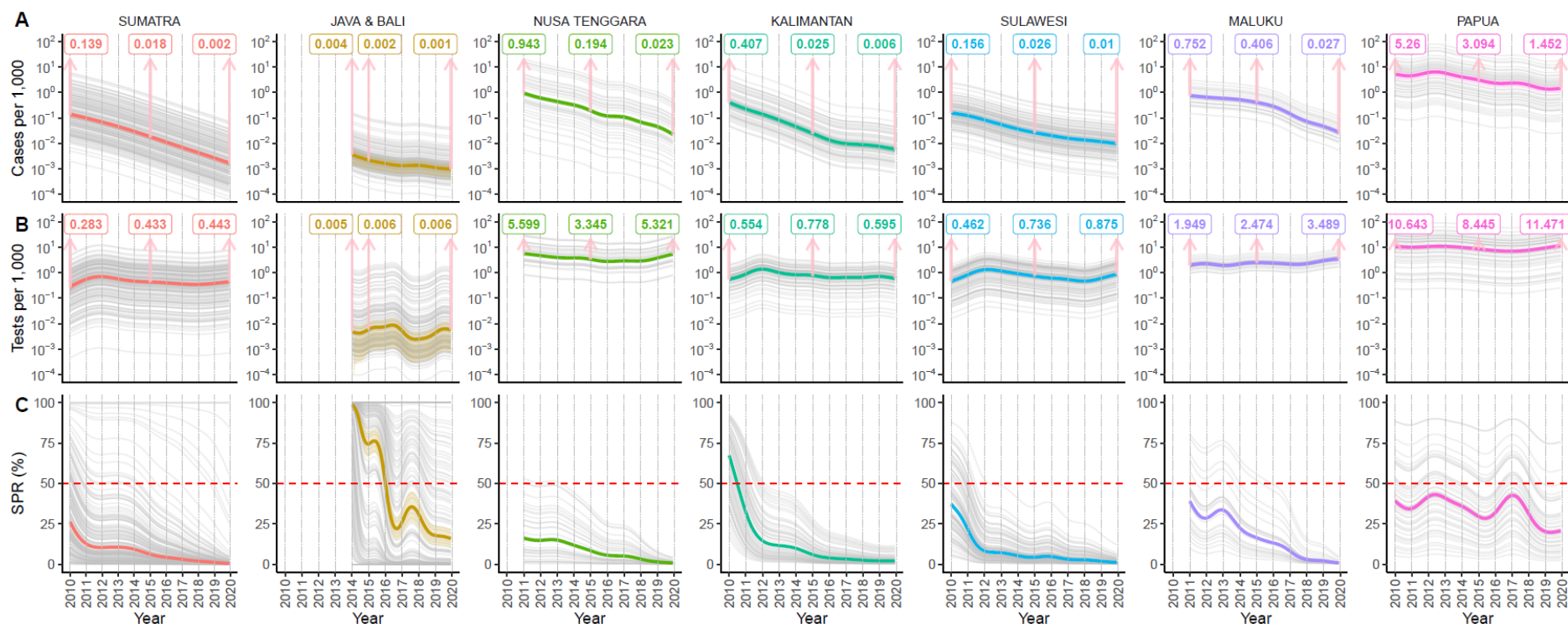


Figure 5.4. Regional-level monthly trends of several malaria metrics. The coloured lines denote the median of modelled region-level trends based on Generalised Additive Models. Shaded areas denote the 95% confidence intervals of the region-level trends in the highlighted region. Grey lines denote modelled district-level trends. A) Number of cases per 1,000 population; B) number of tests per 1,000 population; and C) test positivity ratio. Values shown in the cases and tests per 1,000 population graphs denote the median modelled values from GAMs at the beginning of the first year of reported malaria surveillance data from the region, the beginning of 2015, and the end of 2019.

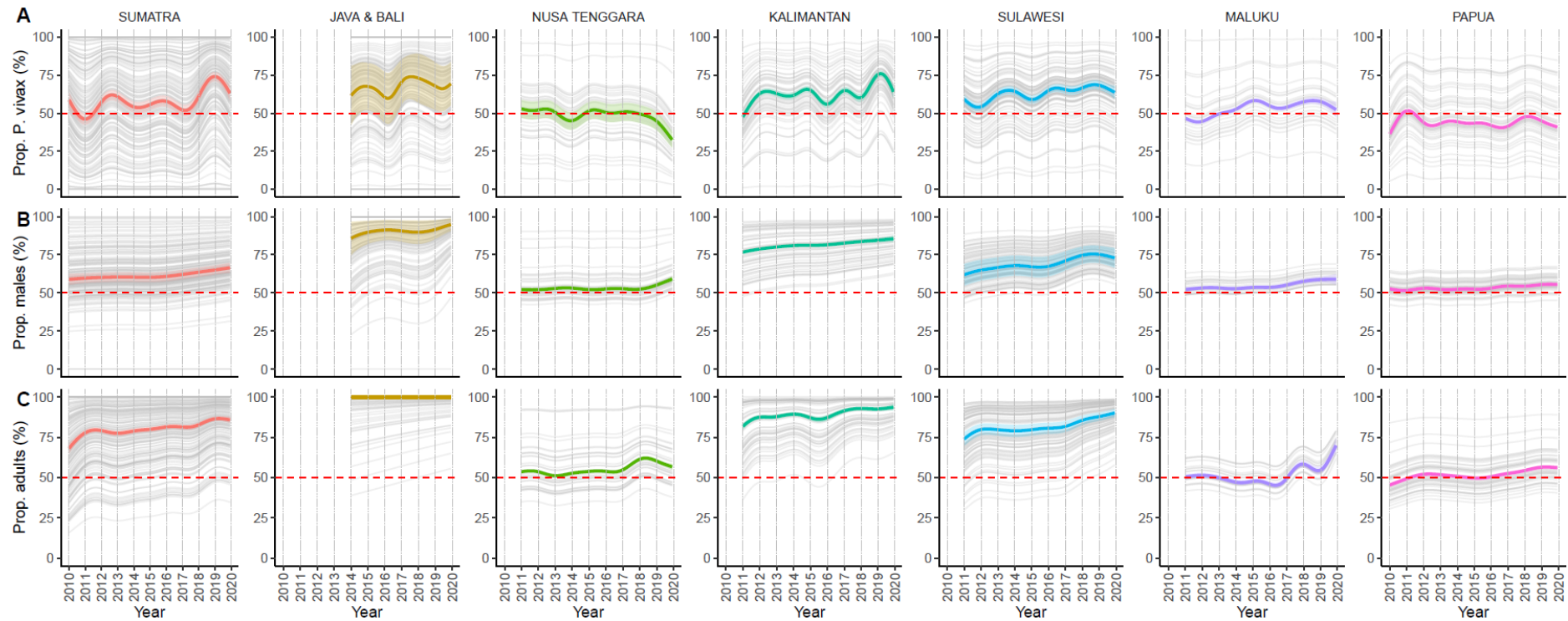


Figure 5.5. Regional-level monthly trends of several malaria case profiles. The coloured lines denote the median of modelled region-level trends based on Generalised Additive Models. Shaded areas denote the 95% confidence intervals of the region-level trends in the highlighted region. Grey lines denote modelled district-level trends. A) Proportions of *P. vivax* cases (including mixed infections with *P. falciparum*); B) proportions of malaria cases in males; and C) proportions of malaria cases in adults (over 15 years old age group).

5.3.3 Measuring correlations and relationships between malaria metrics

As measured by Spearman's rank correlations, the correlation between malaria incidence and TPR varied by region and data type (**Table 5.2** and **Figure 5.6**). Regions with the highest malaria endemicities (Nusa Tenggara, Maluku, and Papua) had higher correlation coefficients when using yearly data compared to monthly data, as shown in **Figure 5.6**. In the Papua region, the correlation coefficient was higher when using yearly data filtered only to include observations with more than 5% ABER (relatively more adequate surveillance efforts). In regions with lower malaria endemicities (Sumatra, Java & Bali, Kalimantan, and Sulawesi), the correlation coefficients were higher when measured using monthly data compared to yearly data. However, the differences between monthly and yearly data estimated correlations were substantially higher in Java and Bali, and Sulawesi regions. Generally, the correlation coefficients using yearly data were higher when only districts with more than 5% ABER were included, as opposed to yearly data from all districts, regardless of their ABER. Scatter plots of malaria incidence per 1,000 population versus TPR for each region and data type are available as **Figures S5.6-S5.8** in the Supplementary Figures section.

GLMs were used to investigate the relationship between malaria endemicity, measured by API per 1,000, and the age of infections. **Figure 5.7** illustrates the relationship between API per 1,000 and the proportion of cases in the population aged 0-4, 5-9, 10-14, and 15 years old and above. **Figure 5.8** shows the overall modelled relationship between API per 1,000 and the proportion of cases by age group. The results indicate that the relationship between malaria endemicity and the age of infections followed the expected pattern, with the proportion of malaria cases in the younger population increasing with higher malaria endemicity; however, the trends varied by region. For example, malaria cases were generally older in the Kalimantan region compared to the modelled relationship. In contrast, malaria cases in Nusa Tenggara and Maluku tended to be younger than the general relationship estimated by the GLM (Figures highlighting each region are available as **Figures S5.12-S5.18** in the Supplementary Figures section).

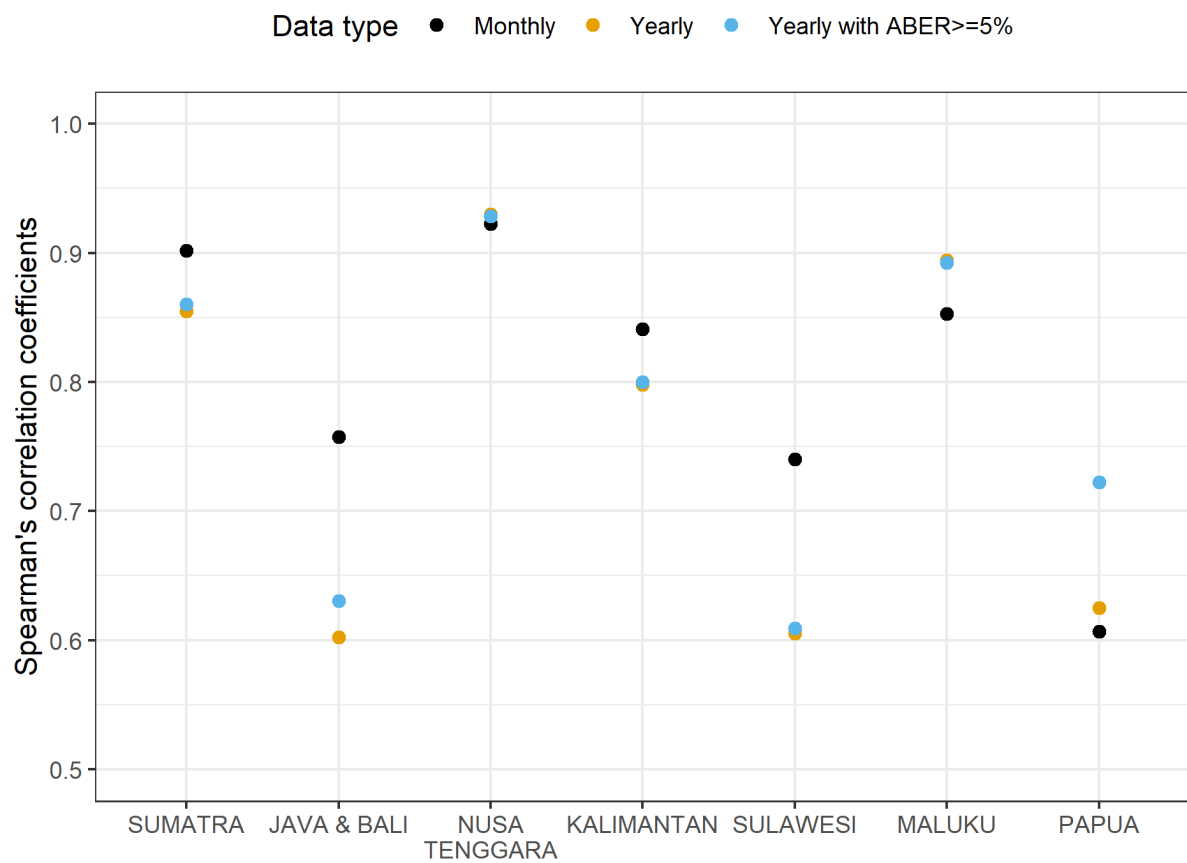


Figure 5.6. Spearman's correlation coefficients between incidence per 1,000 and TPR by region. Correlation coefficients were calculated based on monthly and yearly data (black and orange points, respectively). Blue points denote correlation coefficients based on yearly data, filtered to include only surveillance with ABER $> 5\%$ of the population.

Table 5.2. Spearman's correlation coefficients between incidence per 1,000 and TPR by region and data types used with their corresponding number of observations.

Region	Spearman's correlation coefficients	No. of observations	Data type
Java & Bali	0.757	1031	Monthly
Kalimantan	0.841	4915	Monthly
Maluku	0.853	1959	Monthly
Nusa Tenggara	0.922	3114	Monthly
Papua	0.607	2463	Monthly
Sulawesi	0.740	6962	Monthly
Sumatra	0.902	8862	Monthly
Java & Bali	0.602	91	Yearly
Kalimantan	0.798	420	Yearly
Maluku	0.894	168	Yearly
Nusa Tenggara	0.930	264	Yearly
Papua	0.625	213	Yearly
Sulawesi	0.605	598	Yearly
Sumatra	0.855	756	Yearly
Java & Bali	0.631	76	Yearly with ABER $\geq$ 5%
Kalimantan	0.800	413	Yearly with ABER $\geq$ 5%
Maluku	0.892	157	Yearly with ABER $\geq$ 5%
Nusa Tenggara	0.928	262	Yearly with ABER $\geq$ 5%
Papua	0.722	186	Yearly with ABER $\geq$ 5%
Sulawesi	0.609	591	Yearly with ABER $\geq$ 5%
Sumatra	0.860	746	Yearly with ABER $\geq$ 5%

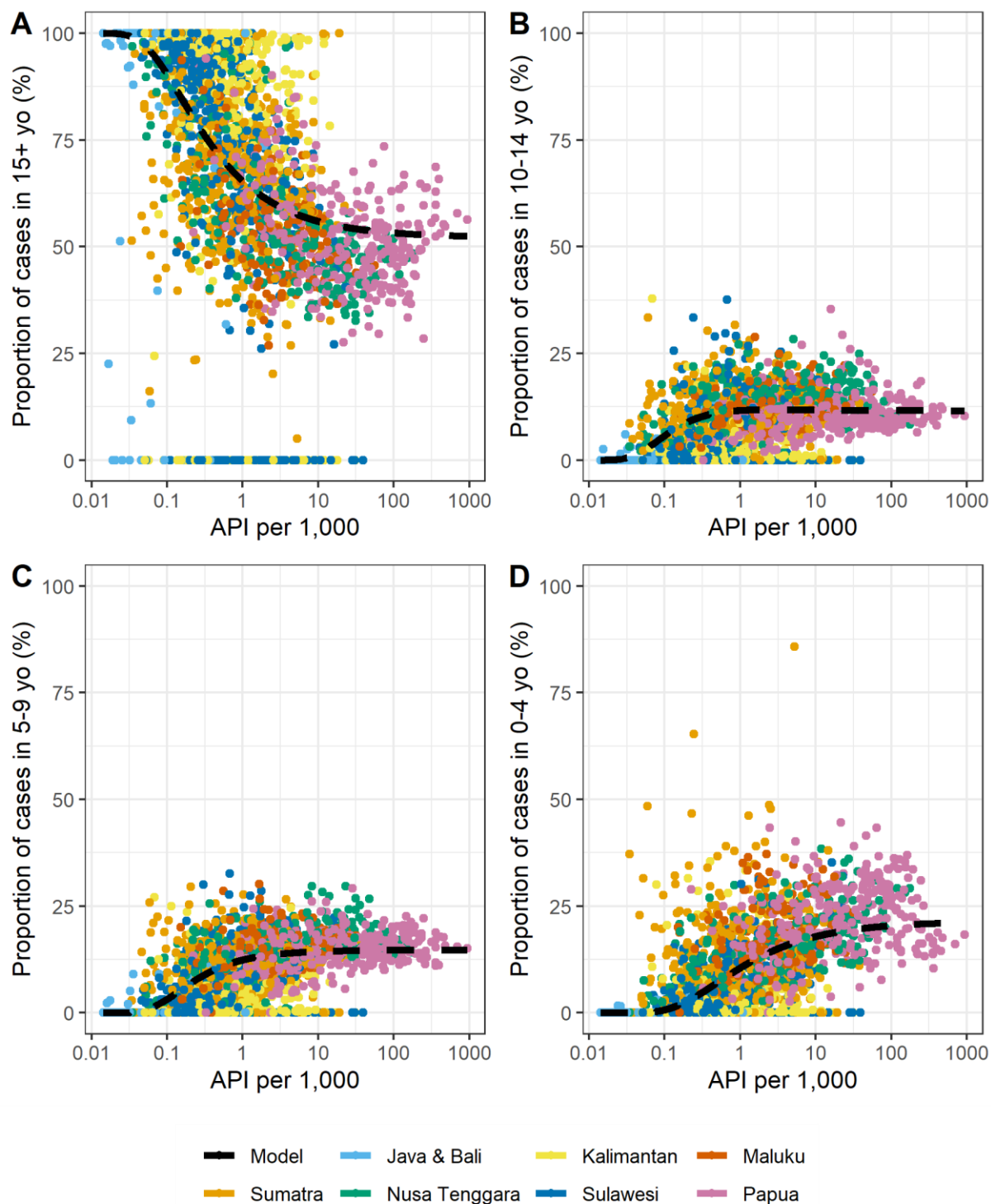


Figure 5.7. Modelled relationships between API per 1,000 and proportion of cases in people aged over 15 (A), 10-14 (B), 5-9 (C), and 0-4 years old (D) with overlaid data from routine surveillance. Dashed lines denote the median of GLM estimates of the relationship. The colours of data points represent regions.

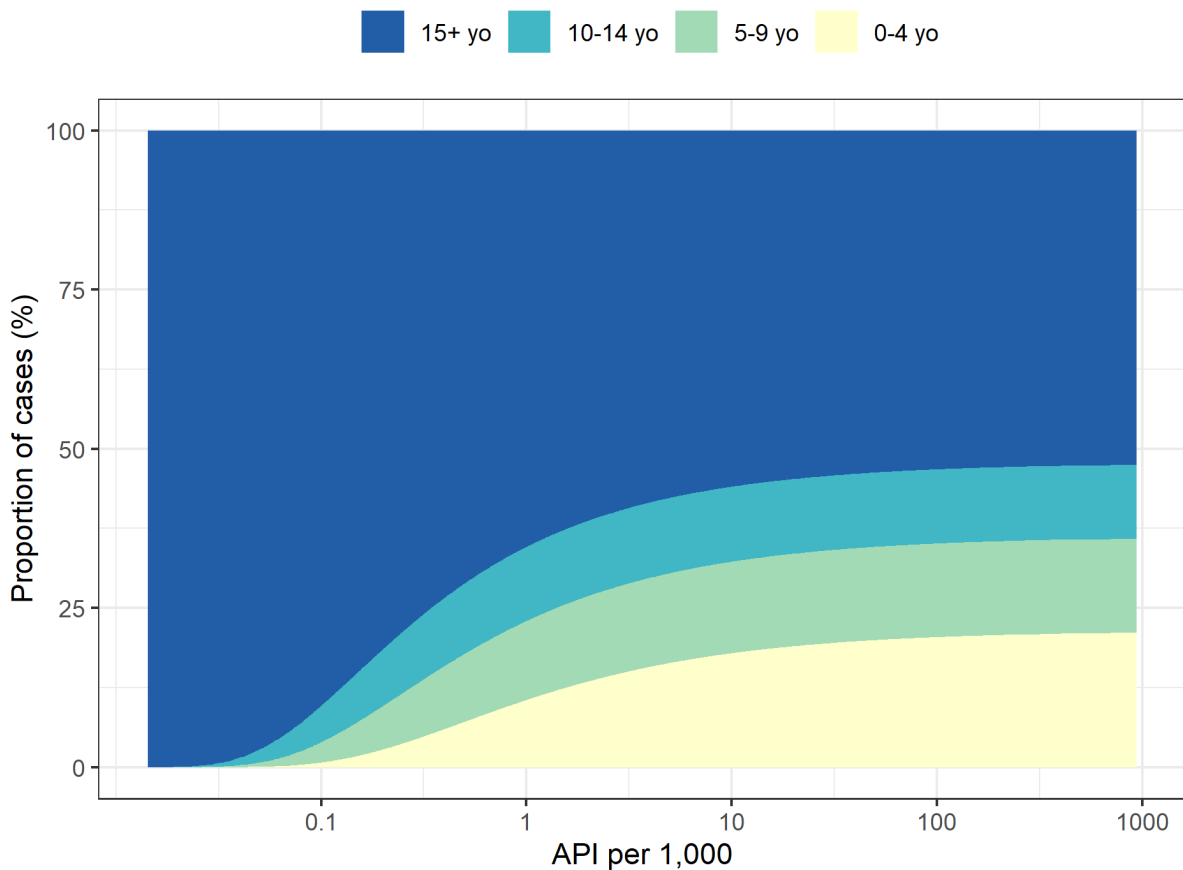


Figure 5.8. Modelled relationship between API per 1,000 and proportion of cases by age group.

5.4 Discussions

The analysis presented in this chapter highlights the dramatic changes in the malaria landscape in Indonesia between 2010 and 2019, with a major shift downwards in malaria cases. While national-level malaria cases have stagnated since 2015, the sub-national trends revealed a steady decline in malaria cases in regions covering more than 95% of the country's population. Furthermore, while regions had differences in malaria transmission at baseline, progress towards malaria elimination in those regions also happened at different paces. Regions with lower baselines experienced larger proportional declines in cases, while the highest reductions in absolute terms occurred in places with higher baselines. Given that more than 90% of reported malaria cases occurred in the Papua region, where only 2% of the population resides, it is clear that the priority for malaria elimination endeavours of Indonesia should be the intensification of control and elimination efforts in Papua, while also maintaining the steady progress in other regions.

With the decline in malaria incidence, there was an increase in the proportion of malaria cases among adults and males. The shifts in age patterns are consistent with the typical sign of sustained declines in transmission (Carneiro et al., 2010; Griffin et al., 2014). In addition, an

increase in the proportion of adult and male cases is typically a sign of occupational-driven exposure, where transmission occurs in high malaria-risk settings, such as forests and mines, far from human settlements (Ekawati et al., 2020; Herdiana et al., 2016; Rahayu et al., 2020). These changes in the profile of cases lead to different priorities faced by different regions in their efforts to continue progressing towards malaria elimination.

Moreover, changes in land-use patterns throughout the decade may have also played a role in influencing malaria trends (CSIRO, 2023; Moyes et al., 2016; van de Straat et al., 2022). Agricultural expansion, deforestation, and other land-use modifications can increase human-vector interactions, potentially affecting malaria transmission dynamics. Alongside these changes, variations in climate factors such as temperature, rainfall, and humidity across different regions of the country and climate variability may have contributed to the observed trends and regional differences (Meteorology, Climatology, and Geophysical Agency of Indonesia, 2022). Further investigation into the interplay of these environmental factors could provide a more nuanced understanding of the changes in malaria incidence observed throughout the decade.

In Java, Kalimantan, and Sulawesi, over 85% of malaria cases were reported in adults, who were predominantly male, indicating that malaria problems in these regions are likely linked to adult workers and importations. For example, in Java, where local malaria transmissions are relatively low, transmission occurs in small clusters, and cross-border malaria and importations of cases from other regions are the main problems, making it difficult to eliminate and maintain elimination in the region (Ahmad et al., 2021; Rejeki et al., 2019, 2022). In West Java province, malaria cases were imported by returning workers from outside Java, with a single district still struggling to eliminate local malaria transmission (Dipa, 2019; Eryando et al., 2012). On the other hand, in Central Java and Yogyakarta provinces, cross-border malaria occurs in the Menoreh Hills, a region located within three districts in two provinces, which poses challenges to malaria elimination efforts in those districts (Ahmad et al., 2021; Rejeki et al., 2019). In Sumatra, Kalimantan, and Sulawesi regions, mobile and migrant populations (MMP), such as indigenous tribal communities, illegal forest workers, and illegal miners, pose a challenge in eliminating local malaria transmission from the regions (World Health Organization, 2022e). A recent assessment by the Indonesia NMCP identified malaria in MMP as the main issue in nine districts in Kalimantan and Sulawesi regions that have shown slow progress towards malaria elimination in the past five years (World Health Organization, 2022e). Finally, the capital relocation project from Jakarta to East Kalimantan might pose an additional risk of increased local transmission in the region due to the influx of malaria-naïve populations, the availability of malaria vectors, and its proximity to malaria-endemic districts (Bin Said et al., 2022).

In Sumatra, despite seeing massive reductions in malaria cases over the decade, the proportion of cases in adults remains slightly lower compared to Java and Bali, Kalimantan, and Sulawesi. A recent study has shown that malaria risks are high among military personnel, forest workers, and miners in the Sumatra region (Fahmi et al., 2022). However, deforestation due to increased mining and plantation activities has also increased malaria risks in the nomadic indigenous population in Sumatra, with malaria prevalence as high as 24% in this population (Plasmanto, 2022). These pockets of high-prevalence indigenous populations are likely the driver of the slightly younger demographics of malaria cases in the Sumatra region, even after massive reductions in the overall number of cases. This highlights the importance of tackling malaria in the indigenous population to progress malaria elimination in this region.

In Nusa Tenggara and Maluku, the age profile of reported malaria cases still indicates a high proportion of community-based transmission, despite a huge decline in malaria cases over the decade. However, due to the differences in the baseline level of malaria transmission compared to Sumatra, Java and Bali, Kalimantan, and Sulawesi, this age profile may be caused by the residual immunity in older populations that will fall as the declines to moderate- and low-level of malaria transmissions occurred relatively recently. This age profile may also be due to pockets of moderate and high endemic districts in the region that dominated the overall profile of malaria cases. In that case, the focus of these regions should be on reducing the districts that still serve as pockets of malaria cases in the region. Papua region has seen huge declines in malaria incidences, but the level of malaria transmission in the region remains high. Although not explored here, socioeconomic factors are still important aspects related to malaria control in these regions. Studies based on the National Basic Health Research (Riskesdas) surveys showed that inequalities and poverty were still among the most important risk factors for malaria in the highest-risk regions of Nusa Tenggara, Maluku, and Papua (Hanandita & Tampubolon, 2016; Hasyim et al., 2019). Therefore, accelerating malaria elimination efforts in these regions would also require improvements in the social determinants of the health of the population.

Furthermore, it is also important to highlight again that Papua was the only region in the country seeing a resurgence of malaria cases in this decade. This resurgence also mirrored the trends observed in the neighbouring country Papua New Guinea (M. Hetzel et al., 2014; M. W. Hetzel et al., 2018), which makes it crucial to explore further whether the drivers of the resurgences in these regions were similar or not. Additionally, when explored further, there were different trajectories in progress towards malaria elimination between the two provinces in the Papua region, Papua Barat and Papua, which will be explored further in **Chapter 7** of this thesis.

The estimated correlations between malaria incidence and TPR revealed that changes in malaria transmission were consistently captured in agreement with both monthly and yearly metrics in most regions, including Sumatra, Nusa Tenggara, Kalimantan, and Sulawesi. However, in Java and Bali, as well as Sulawesi, inconsistent correlations between yearly and monthly data may be due to inconsistent testing and reporting efforts each month. In Papua, testing efforts need to be increased across all districts as correlations between the metrics were low compared to other regions.

This study does not explore and analyse further the emergence of zoonotic malaria infections, *P. knowlesi*, in the country from the routine data. Due to increased forest activities, risks of infection to zoonotic malaria increased, especially near the forest areas of the Sumatra and Kalimantan regions (Figtree et al., 2010; C. A. Gunawan et al., 2022; Herdiana et al., 2016; Nainggolan et al., 2022). As of 2019, the number of reported *P. knowlesi* infections in the country remains relatively small (Fajariyani & Anggraeni, 2020). On the other hand, in the neighbouring country Malaysia, especially in their Malaysian Borneo (Kalimantan) side, *P. knowlesi* is now the dominant malaria infection, accounting for more than 90% of their total malaria incidences (Chin et al., 2021). The apparent difference in the epidemiology of *P. knowlesi* in both countries is also found in a recent survey in one district in Kalimantan, neighbouring Malaysian Borneo (Sugiarto et al., 2022). More extensive surveillance is needed to confirm that *P. knowlesi* is currently not a threat to malaria elimination efforts in the country. Therefore, innovations in diagnostics and continued human capacity strengthening for malaria diagnostics in areas in high-risk of *P. knowlesi* infections are needed due to many misdiagnosed infections in the past (Barber et al., 2013; Coutrier et al., 2018). Increasing awareness of this issue, especially for high-risk populations, is important to prevent more cases of *P. knowlesi*.

Finally, this chapter focuses on analysing region-level trends and relationships of multiple malaria metrics, which shows how huge progress towards malaria elimination had been made during the 2010-2019 decade. Furthermore, in this chapter, I showed how by analysing multiple metrics collectively, we could get better confidence in trends we see in the malaria surveillance data by providing complementary contexts of how malaria dynamics relate to each of those metrics. As progress toward malaria elimination has been made throughout 2010-2019, malaria elimination efforts remain far from over in the country. The diverse malaria transmission landscape across the country means locally tailored efforts are needed to address specific issues facing each region. Additionally, between-district cooperations and partnerships must be strengthened to tackle the importations of malaria, especially to areas already eliminating malaria or near elimination.

5.5 Conclusions

The landscape of malaria in Indonesia has shifted dramatically over the last decade. The changes are not only in terms of how many people are sick with malaria, but also who are being impacted by the disease. With cases shifting towards older populations and males, we are seeing signatures of transmission landscapes that are moving towards elimination. This analysis has shown that the next phase of the malaria control and elimination program in Indonesia requires a more targeted approach both in terms of where malaria remains the highest and which populations increasingly drive the transmission (i.e., older and male). The next step of the work is to look at the role of interventions in the decline of malaria over the last decade.

Chapter 6: Were long-lasting insecticidal mosquito net mass distribution campaigns the driver of declines of malaria cases in Indonesia?

This chapter aims to evaluate the plausibility of the hypothesis that the introduction of long-lasting insecticidal mosquito net (LLIN) mass distribution campaigns (or mass LLIN campaigns) that occurred extensively across Indonesia between 2010-2019 was the main driver of the decline in malaria cases across the country. The analysis was done at the regional level, specifically within districts that conducted LLIN mass distribution campaigns during 2010-2019. I analysed patterns of malaria incidence rates and test positivity ratios (TPRs) using a changepoint analysis algorithm to determine whether declines in those metrics coincided with the timing of the mass LLIN campaigns and were consistent across all regions. This analysis of incidence patterns was guided by the plausible traits of malaria incidence trends generated by mathematical models that cover ranges of LLIN mass campaign implementation scenarios. A mini literature review was also conducted to provide evidence from past studies and experiments on the plausibility of LLINs as the driver of the decline of malaria cases in the population. Finally, using the Bradford Hill criteria for causality as guidelines for the evidence assessment, the evidence gathered from the data analysis and literature review was synthesised to conclude whether it is plausible to say that mass LLIN campaigns were the driver of the massive declines in malaria cases across the country over the decade of 2010-2019.

6.1 Introductions

6.1.1 Background

Ensuring universal coverage of ITN or LLIN for all people at risk of malaria is one of the pillars of the Global Technical Strategy (GTS) for Malaria 2016-2030 (World Health Organization, 2021a). To achieve and maintain universal coverage of LLIN, Indonesia applied a combination of LLIN mass distribution campaigns at the district level, targeted LLIN distributions in focus (or high-endemic) villages, a continuous distribution of LLIN through antenatal care (ANC) for pregnant women, and incidental LLIN distributions as a response to a malaria outbreak event or as a part of epidemiological investigations of cases (Ministry of Health of the Republic of Indonesia, 2020c; World Health Organization, 2017). The Global Fund usually funded the LLINs distributed during sub-national LLIN mass distribution campaigns and targeted distributions in Indonesia. The nets for routine and incidental distributions were often funded

using the government's budget. Mass campaigns were done in districts with annual parasite incidence (API) ≥ 5 per 1,000 population, categorised as high-endemic districts. In the moderate endemic districts (API 1-5 per 1,000 population), targeted distributions of LLIN were conducted, aiming at villages categorised as local malaria focus (Ministry of Health of the Republic of Indonesia, 2020c).

As discussed in the previous chapter, malaria cases declined in all regions of Indonesia during 2010-2019. Throughout this period, Indonesia also saw accelerations in multiple aspects of their malaria control efforts, one of them being the scale-up of insecticide-treated mosquito net or ITN (in the form of long-lasting insecticidal mosquito net/LLIN) distributions through mass distribution campaigns and routine distribution programmes (Sitohang et al., 2018). However, the impact evaluation of these interventions often remains outstanding. Such evaluations are needed to understand, for example, whether those interventions positively or negatively impacted the population, contributed directly or indirectly to the changes in health outcomes, and worked similarly across all settings (Peersman, 2015). For example, in Africa, a modelling study showed that increased ITN coverages and usages were the main drivers of the decline in malaria prevalence and clinical incidence in the continent (Bhatt et al., 2015). Impact evaluation is also important from the funders' perspective (i.e., the government themselves and donors) (Yé et al., 2017). The funders made huge investments in implementing those scale-ups; consequently, it is important to ensure that if changes in the health outcome are achieved, they can be attributed to the program. Therefore, impact evaluation is important in providing evidence to support the program's continuation or replication elsewhere.

Randomised controlled trials are often considered the gold standard for evaluating the impact of public health interventions. However, they may be unethical or inappropriate for interventions that have been proven effective or implemented at a large scale, whether in controlled settings or other populations (e.g., increased usage of LLIN through mass distribution campaigns). Methods such as quasi-experimental design can be used to evaluate and demonstrate the plausibility of a causal link between an intervention and an outcome of a routine program. However, it is impossible to find proper counterfactuals in a setting where interventions were done on a large scale across all populations with similar settings. In the context of these issues, analysis and exploration of routinely collected surveillance data offer an alternative, albeit an imperfect one, for evaluating the impact of control programs. Such data is frequently prone to limitations and biases (described in detail in previous chapters), which means it is often overlooked in preference to cross-sectional surveys as the primary data for impact evaluations (Ashton et al., 2017). However, conducting surveys can be costly and complex, while routine surveillance data are often readily available and may provide some

insight into the impact of control programs, though careful interpretation is required. Moreover, Ashton et al. reviewed several methods for impact evaluations of malaria control programs that utilised routine malaria data, including pre-post intervention comparison, descriptive analyses of trends, interrupted time series, and subnational dose-response (Ashton et al., 2017).

Furthermore, when evaluating the impact of interventions, especially in the context of malaria intervention scale-up, we need to consider appropriate methods to ensure that we can appropriately attribute the health outcome impact to the particular intervention we evaluate. Yé et al. developed a framework for evaluating the plausibility of a causal link between scale-ups of malaria control and interventions and their health impact (Yé et al., 2017). Their work used the framework to identify plausible contributions of malaria interventions on malaria morbidity and mortality, considering the Bradford Hill criteria for causality.

6.1.2 Plausibility design to evaluate the impact of malaria interventions

Evaluating the impact of LLIN mass distribution campaigns using experimental or quasi-experimental study designs is difficult due to challenges in randomisation and finding counterfactual scenarios. Yé et al. proposed a pre-post reflexive control study design, which is also known as the plausibility study design, as an alternative to experimental (and quasi-experimental) studies for assessing the impact of interventions that have already proven efficacious on malaria outcomes, such as LLIN mass distribution campaign (Yé et al., 2017). They argued that unless other contextual factors likely to explain the reductions in burden existed, it is plausible that scale-up of interventions that have already proven efficacious on malaria outcomes could be the driver of the observed reductions in malaria burden. The evidence generated from the plausibility design can be strengthened if the baseline of the burden before the scale-up of interventions can be established, assuming that in the absence of interventions, the burden trends before the scale-up would have continued.

The plausibility design can take advantage of the Bradford Hill causality criteria, as also defined in the Yé et al. framework (Yé et al., 2017), by using it as a set of guidelines for impact evaluation. **Table 6.1** shows the list of criteria, namely: strength of association, consistency, specificity, temporality, gradient, plausibility, coherence, experiment, and analogy, along with their general definitions, adapted from Yé et al. (Yé et al., 2017). While there are reservations related to the use of such criteria to evaluate causality, especially when treating them as a mere checklist of evidence (Rothman & Greenland, 2005), I argue that in the context of evaluating the impact of interventions that have already proven efficacious, these criteria provide a systematic tool to gather evidence related to impact evaluation of the implementation

of such interventions, in addition to critically explaining the epidemiological context surrounding the implementation.

Table 6.1. The Bradford Hill causality criteria for application to plausibility assessment.

Criteria	Descriptions
Strength of association	Strong associations are more likely to be causal than weaker associations.
Consistency	Observing similar associations across different populations and over time increases the likelihood of causal relationships.
Specificity	Observing associations specific to outcomes of interest among specific groups increases the likelihood of causal relationships.
Temporality	Changes in the outcomes of interest must be preceded by the changes in the program.
Gradient	Changes in the outcomes of interest increase when the intensity of program exposure increases.
Plausibility	There is a plausible biological mechanism that links the exposure to intervention with the outcomes of interest.
Coherence	Supporting literature or substantive knowledge that supports the conclusion on the assessed causal relationships.
Experiment	Prior experimental studies that support the conclusion on the assessed causal relationships.
Analogy	Similar results have been obtained from similar programs operating in the past or in other settings.

6.1.3 What is a plausible impact of LLINs? – insights from models.

Using a mechanistic model of malaria (see Chapter 1 supplementary materials for the details of the model and Chapter 6 supplementary materials for the details of the model simulation process, both in **the Appendix**), the biological plausibility of LLIN impacts on malaria clinical incidence at the population level in the context of LLIN distributions through mass campaigns were assessed. **Figure 6.1** presents mathematical model scenario simulations that provide insights into what trends we might expect to see in the context of mass LLIN campaigns and how these relate to the Bradford Hill criteria for assessing LLIN impacts.

- **Figure 6.1A** compares the trends of the baseline scenario simulation (without any interventions) to the scale-up of the artemisinin-based combination therapy (ACT) scenario and a mass LLIN campaign scenario. In the mass LLIN campaign scenario, a big impact occurred soon after the campaign, followed by a resurgence in malaria incidence to the baseline equilibrium as no other intervention was in place. ACT scale-

up, which was maintained continuously, generated a smaller but more lasting impact on malaria incidence, creating a new equilibrium.

- **Figure 6.1B** once again highlights how substantial impact occurs rapidly after the implementation of mass campaigns – and the later the campaign is conducted, the later the impact is seen on malaria incidence.
- **Figure 6.1C** shows how multiple mass LLIN campaigns affect malaria incidence at the population level. Resurgences between campaigns are observed, and a return to the pre-LLIN campaign baseline is expected when the strategy is not maintained. The levels reached in subsequent LLIN mass campaigns are then determined by the levels of effective coverage such campaigns reach (e.g., if a second campaign has lower effective coverage, malaria levels may not reduce to the same minima achieved following the first campaign). However, in the context of multiple campaigns achieving similar effective coverage levels, LLIN campaigns alone are unlikely to produce steady progress towards elimination. Instead, they would be expected to lead to an approximate equilibrium pattern across cycles. In the context where LLINs are the only factor affecting incidence, it would be expected that the malaria level would return to baseline, though, due to the relatively slow decline in effectiveness, over a slower timeframe than the initial decline following the initial implementation of the intervention.

These complex relationships between the distribution of LLINs and subsequent trends mean that plausibility assessment using any time series of incidence, even one that is perfectly observed, is a highly difficult task. In light of this, in this chapter, I attempt to develop a semi-quantitative framework which uses a recently developed algorithm designed to decompose time series into a parsimonious set of key ‘changepoints’. Based on the application of these methods to simulated data (see above), routine cases reporting series were decomposed into segments at which the statistical properties of the time series change (see methods section for full details).

6.1.4 Aims

This chapter combined analysis of mathematical model simulations and routine malaria surveillance data from the Indonesia Nasional Malaria Control Program (NMCP), along with literature searches, with aims to:

1. Determine the timing of the changepoints of malaria incidence rate and test positivity ratio using a changepoint analysis algorithm.
2. Evaluate the impact of LLIN mass distribution campaigns on malaria morbidity and transmission in Indonesia using a plausibility framework that incorporates the Bradford Hill causality criteria and the above insights from modelling to assess whether it is

plausible to attribute the changes in malaria morbidity and transmission to the mass LLIN campaigns conducted between 2010 and 2019.

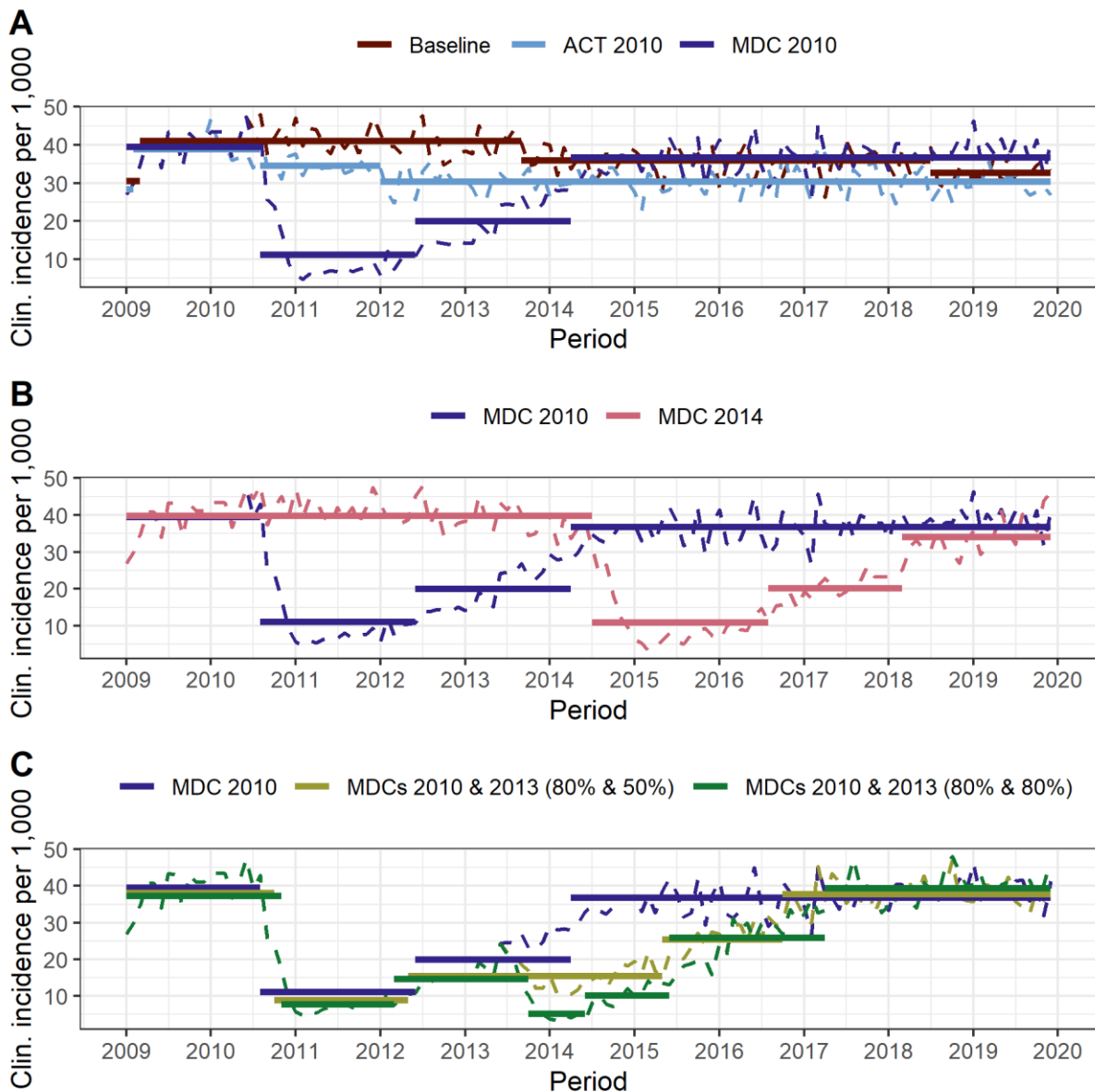


Figure 6.1. Implementations of changepoint algorithm to simulated scenarios of malaria clinical incidence per 1,000. A) Comparison of baseline, ACT only, and mass distribution campaign only scenarios. MDC in the legends means mass distribution campaign; B) Early and later mass distribution campaign scenarios; C) Single and multi year mass distribution campaigns scenarios.

6.2 Data and methods

6.2.1 Data

6.2.1.1 LLINs distributions data

Data on yearly district-level LLIN distribution were obtained from the National Malaria Control Program (NMCP), Ministry of Health of the Republic of Indonesia. The funding sources of LLINs distributed were provided in the data (i.e., government-funded nets or the Global Fund-

funded nets). The LLIN mass distribution campaign was defined as a distribution of LLINs funded by the Global Fund that achieved >50% coverage in a single district within a year. On average, each distributed LLIN can be used by two people simultaneously. However, when planning for LLIN procurement, calculations of LLIN coverages must account for households with an odd number of residents. To account for this factor, WHO recommends an overall ratio of one LLIN for every 1.8 persons in the target population (Bertozzi-Villa et al., 2021; Kilian et al., 2010; World Health Organization, 2017). Therefore, the proportion of people receiving a new LLIN each year from a distribution program, or the LLIN coverage, was calculated by:

$$LLIN\ coverage = \frac{\# LLINs\ distributed \times 1.8}{Total\ population}$$

Within a region, districts conducting LLIN mass distribution campaigns were further grouped based on the years in which the campaigns were conducted (e.g., a group of districts conducting mass distribution campaigns in 2011). **Table 6.2** shows mass LLIN campaign groups for each region used in the analysis. The district-level map, coloured by the years of mass LLIN campaigns, is shown in **Figure 6.2**. The names of the districts conducting the campaigns within each group in each region are listed in **Table S6.1**. Dogiyai and Deiyai, the two districts in the Papua region that conducted mass LLIN campaigns only in 2014, were excluded from the analysis as they only had malaria incidence data reported starting in 2015.

Table 6.2. Groups of years of LLIN mass distribution campaigns conducted in each region.

Region	Years conducting mass LLIN campaigns
Kalimantan	1. 2010 2. 2011
Sulawesi	1. 2011 2. 2011 & 2014
Sumatra	1. 2014
Nusa Tenggara	1. 2014 2. 2014 & 2017 3. 2016
Maluku	1. 2014 & 2016 2. 2014 & 2017 3. 2016
Papua	1. 2014 & 2017 2. 2017

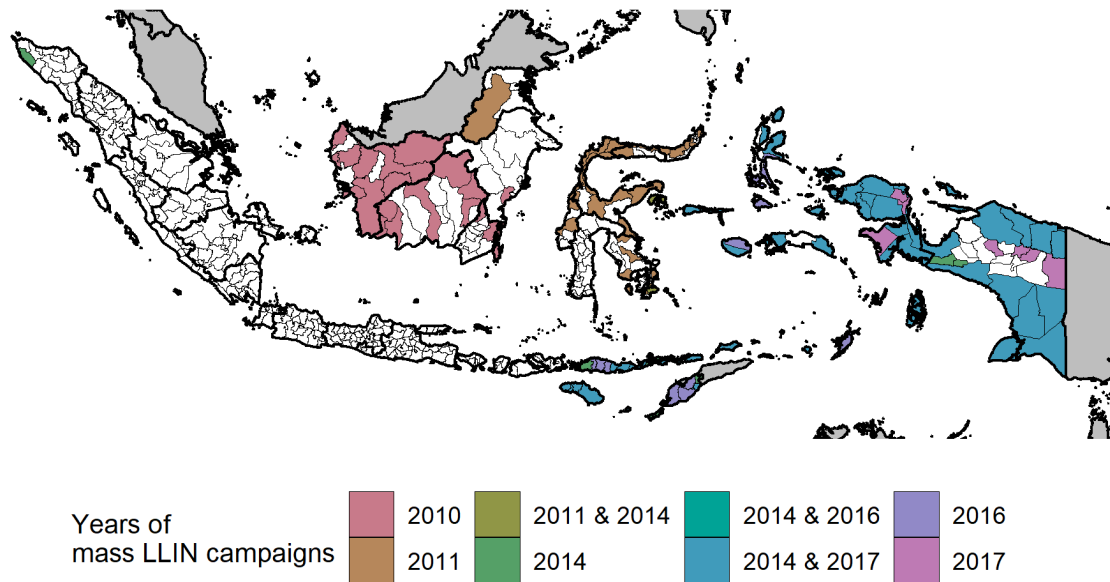


Figure 6.2. The map of districts in Indonesia coloured by years conducting mass LLIN campaigns during the 2010-2019 period. The white shaded polygons indicate districts that did not conduct any mass LLIN campaigns throughout 2010-2019. The grey shaded polygons denote the territories of neighbouring countries.

6.2.1.2 Malaria incidence and test positivity ratio data

District-level routine monthly malaria surveillance data from 2010 to 2019 were obtained from the NMCP. I used the monthly incidence rate per 1,000 population (IR per 1,000) and test positivity ratio (TPR) as metrics representing malaria morbidity and transmission intensity, respectively. District-level monthly IR per 1,000 and TPR were calculated for all districts conducting LLIN mass distribution campaigns. The trends for each metric were observed in each region, with districts further grouped by the years of mass LLIN campaigns conducted. To represent the subgroup trends of each region, the median value of each metric from all districts within each mass LLIN campaign subgroup was calculated for each month. Data imputations were conducted when missing data occurred by generating a random number based on the truncated Normal distribution with mean and standard deviation calculated from the 10 neighbouring data points (e.g., 5 before and 5 after).

6.2.2 Methods

6.2.2.1 Evaluating the impact of LLIN mass distribution campaigns using a plausibility framework with Bradford Hill causality criteria

To explore the plausibility of LLIN mass distribution campaigns as the major cause of declines in malaria cases in Indonesia, I used the plausibility design framework (as elaborated in the **introduction section 6.1.2**), which involves two analysis steps: 1) conducting a literature search of relevant studies; and 2) conducting data analysis of available data. The literature search step covers the coherence, experiment, and analogy criteria evaluation of the Bradford

Hill framework. This involves examining past studies that provide evidence of the impact of LLIN on the reductions of malaria clinical incidence from experimental studies or evaluation of similar interventions (i.e., mass LLIN campaigns) elsewhere.

My analysis of the routine surveillance data addresses the strength of association, consistency, specificity, temporality, and gradient criteria of the Bradford Hill framework. Informed by the insights from the models above, I generate the following sets of semi-quantitative criteria by which to assess the extent to which the time series data are displaying plausible traits associated with a substantial impact of LLINs:

1. **Temporality:** Did a changepoint to a lower level occur within a year of the first LLIN campaign?
2. **Specificity:** If such a changepoint existed, did it represent the first in the time series and/or the largest in the dataset?
3. **Gradient:** Defining a specific range for the magnitude of this changepoint is difficult as studies are rarely able to capture dynamics over such short timeframes. However, based upon the modelling insights above, larger reductions relative to pre-LLIN distribution were deemed as providing greater plausibility for the association.
4. **Consistency:** Allied to temporality, were regions implementing mass campaigns later those which saw changepoint reductions occurring later? Did subsequent changepoints correlate with likely changes in effective coverage based upon subsequent patterns of LLIN distribution?

Overall, the evidence gathered from the analysis of literature, model simulations, and routine surveillance data were combined to provide a comprehensive assessment of the plausibility of mass LLIN campaigns as the main driver contributing to the observed declines in malaria cases in Indonesia.

6.2.2.2 Changepoint analysis algorithm

Killick et al. defined changepoint analysis as the identification of points within a dataset where the statistical properties change (Killick et al., 2012). Those changes may be in the form of mean, variance, or any other statistical properties from one segment to the other. If we have a time series data of $y = (y_1, y_2, \dots, y_n)$, the changepoint analysis aims to find the number of changepoints, m , as well as their positions $\tau = (\tau_1, \tau_2, \dots, \tau_m)$. The changepoints are ordered such that $\tau_i < \tau_j$ if, and only if, $i < j$. τ_i is an integer and that $0 = \tau_1 < \tau_2 < \dots < \tau_m < \tau_{m+1} = n$. Thus the m changepoints split the time series data into $m + 1$ segments. The i^{th} segment of the data contains $y_{\tau_{i-1}+1:\tau_i}$. The best segmentation for a dataset is the one that minimised a penalised cost function (e.g., $\sum_{i=1}^{m+1} [C(y_{\tau_{i-1}+1:\tau_i})] + \beta f(m)$, where C is a cost function of a

segment and $\beta f(m)$ is a penalty to avoid overfitting). The cost function is defined as twice the negative log-likelihood of the assumed distribution of the data. However, to find the changepoints of the malaria metric time series, I used the nonparametric approach by Haynes et al. (Haynes et al., 2017) and Zou et al. (Zou et al., 2014), using the negative nonparametric log-likelihood of data within each segment as the cost function. The nonparametric method is suitable for detection of any changes in the distributions between successive segments and less prone to model misspecification compared to the parametric methods.

The nonparametric approach utilises the empirical cumulative distribution function (CDF) of the dataset. For the i^{th} segment, the empirical CDF ($\hat{F}_i(t)$) is defined as $\frac{1}{\tau_i - \tau_{i-1}} \times (\sum_{j=\tau_{i-1}+1}^{\tau_i} 1\{x_j < t\} + 0.5 \times 1\{x_j = t\})$. For a fixed t and n independent and identically distributed data points with CDF $F(t)$, the empirical CDF will satisfy $n\hat{F}(t) \sim \text{Binomial}(n, F(t))$. The cost function for segment i , which is the negative of the log-likelihood of the empirical distribution of the segment ($-L_{np}(x_{\tau_{i-1}+1:\tau_i}|t)$), is defined as: $-(\tau_i - \tau_{i-1}) \times [\hat{F}_i(t) \log \hat{F}_i(t) + (1 - \hat{F}_i(t)) \log(1 - \hat{F}_i(t))]$. The cost of a segmentation is defined as the sum of the segment costs. Thus, for a segmentation of data with m changepoints, we minimise the cost function: $-\sum_{i=1}^{m+1} L_{np}(x_{\tau_{i-1}+1:\tau_i}|t)$.

I used a changepoint search approach using the pruned exact linear time (PELT) method with a cost based on the empirical distribution to detect changepoints within a dataset (Haynes et al., 2017; Killick et al., 2012). The method was implemented using the `changepoint.np` package in R statistical software (Haynes & Killick, 2021).

6.3 Results

6.3.1 Evidence from literature searches

Table 6.3 shows a list of literature and their summaries, providing evidence supporting the coherence, experiment, and analogy aspects of the Bradford Hill causality criteria. These studies highlight the role of ITN (and LLIN) usage in reducing the clinical incidence of malaria in various countries with different transmission characteristics and settings. The literature encompasses a range of study types, including experimental studies, cluster-randomised control trials (cRCTs), and modelling studies (Bhatt et al., 2015; Henry et al., 2005; Marbiah et al., 1998; Nevill et al., 1996; Pryce et al., 2018; Rowland et al., 1996; Smithuis et al., 2013; Sochantha et al., 2006).

These studies showed that LLIN interventions have led to reductions in the incidence of *P. falciparum* malaria ranging from 28% to 61%, while the reductions in *P. vivax* incidence ranging from 39% to 42%. The malaria incidence classifications used in these studies range

from uncomplicated clinical cases to severe cases, with several studies focused on malaria incidence in children under 5. Additionally, two studies utilising longitudinal routine malaria surveillance data in Madagascar and Malawi showed the impact of mass LLIN campaigns in reducing malaria cases. However, in these studies, the authors also observed resurgences in malaria incidence in the second year following the mass LLIN campaigns. (Girond et al., 2018; Topazian et al., 2021).

Table 6.3. Literature search for Bradford Hill criteria evidence.

Criteria	Sources	Conclusions
Coherence	(Pryce et al., 2018)	A Cochrane Review with an aim to assess the impact of ITNs on mortality and malaria morbidity. The meta-analysis showed that Randomised Controlled Trials (RCTs)/Cluster-randomised Controlled Trials (cRCTs) of ITNs reduce the incidence of uncomplicated <i>P. falciparum</i> and <i>P. vivax</i> malaria by 45% and 39% compared to the no-net control, respectively. The review also found that ITNs reduce the incidence of severe malaria episodes by 44% compared to the no-net control.
	(Bhatt et al., 2015)	A modelling study showed that the incidence of clinical <i>P. falciparum</i> malaria in Africa was reduced by 40% between 2000 and 2015 with ITNs estimated as the largest contributor.
Experiment	(Henry et al., 2005)	cRCT of ITN vs no ITN in Côte d'Ivoire showed a reduction of clinical incidence of <i>P. falciparum</i> malaria by 56% in children under 5.
	(Marbiah et al., 1998)	cRCT of ITN vs no ITN in Sierra Leone showed a reduction of clinical incidence of <i>P. falciparum</i> malaria by 49% in children aged 3 months to 6 years old.

	(Nevill et al., 1996)	cRCT of ITN vs no ITN in Kenya showed a reduction of severe incidence of <i>P. falciparum</i> malaria by 44% in children under 5.
	(Rowland et al., 1996)	Individual RCT of ITN vs no ITN in Afghan refugee villages in Pakistan showed a reduction of clinical incidence of <i>P. falciparum</i> and <i>P. vivax</i> by 61% and 42%, respectively.
	(Smithuis et al., 2013)	cRCT of ITN vs no ITN in Myanmar, where the main vector bites early in the evening, showed a non-statistically significant reduction of clinical incidence of <i>P. falciparum</i> and <i>P. vivax</i> malaria in children under 10. The effect is higher in areas with a higher incidence of malaria.
	(Sochantha et al., 2006)	cRCT of ITN vs no ITN in Cambodia showed a reduction of clinical incidence of <i>P. falciparum</i> malaria by 28%.
Analogy	(Girond et al., 2018)	A longitudinal study in Madagascar found that malaria cases dropped after LLIN mass distribution campaigns. However, resurgences in malaria cases were found from the second year after the campaign.
	(Topazian et al., 2021)	A longitudinal study in Malawi found that malaria incidences dropped after LLIN mass distribution campaigns. However, malaria incidences resurged in the second year since the campaign.

6.3.2 Evidence from routine data analysed using the changepoint analysis algorithm

I implemented changepoint analysis to trajectories of monthly malaria IR per 1,000 (**Figure 6.3A**) and TPR (**Figure 6.3B**) from routine surveillance data. The figures show the graphical representations of the changepoints detected and segments constructed by the algorithm,

grouped by region and the year(s) in which a subgroup of districts within the region implemented LLIN mass distribution campaigns. **Table 6.4** and **Table 6.5** summarise the observed timing of the changepoints and the changes in properties of the constructed segments based on changepoints that coincided with the year of mass LLIN campaigns for IR per 1,000 and TPR, respectively.

As **Figure 6.3** shows, there was a generally clear temporal trend of changepoints occurring sooner in regions where mass LLINs campaigns were distributed earlier (e.g., Kalimantan and Sulawesi), in contrast to regions, such as Maluku and Papua, where their first LLIN mass campaigns were implemented later. However, compared to the regions implementing mass LLIN campaigns earlier, IR per 1,000 and TPR levels in regions with later implementation remained largely similar to those observed in 2009.

In terms of the gradient of change of the metrics observed, **Figure 6.3** also shows that new segments created during LLIN campaigns have lower values than their previous segments. These changepoints of segments observed also occurred during the period of high LLIN distributions, mainly the year of LLIN campaigns, showing that smaller scale-ups occurring earlier did not have impacts as significant as the larger campaigns in each subgroup. **Figure 6.4** shows the timing of changepoints of all regions by type of metrics (IR per 1,000 and TPR), highlighting changepoints occurred during the mass LLIN campaign years or within a maximum period of three months into the subsequent year to account for potential changepoints resulting from late distributions. This summary thereby represents the temporality criterion. **Table 6.6** summarises the frequency of changepoints that occurred during the campaign years. Overall, it was observed that changepoints during the mass LLIN campaign years occurred more frequently in TPR than IR per 1,000.

The average values of those segments are also lower than their previous segments, showing similar patterns to those shown in the analysis of simulated models. The gradient of reductions of the average values of those segments ranged from 45% to 82% for IR per 1,000 and 25% to 82% for TPR. The 2014 & 2017 mass campaigns subgroup from the Papua region, comprising some districts with the highest malaria endemicity in the country, has the lowest gradient of change for the TPR with 25%, which changepoint also occurred the year before the campaign in 2014 without further change during the year of the campaign. Their gradient of change for incidence rate is the second lowest with 48%, only below the 2011 mass campaign subgroup from the Kalimantan region.

In terms of the long-term trends following a single LLIN mass campaign and multiple LLIN mass campaigns, most subgroups showed continued declining trends following the first LLIN campaign, even when only a single mass campaign was conducted, or LLIN distribution

coverage was lower during their second campaign. These observed patterns differed from the expected patterns based on the model simulations for those scenarios. However, there were instances where the patterns following the first campaigns were aligned with the model simulations. For example, in the 2014 & 2016 LLIN campaigns subgroup in Maluku, both IR per 1,000 and TPR patterns showed continued declining trends following higher LLIN coverage during their second mass LLIN campaign in 2016. Additionally, in the Kalimantan region's 2011 mass campaign subgroup, a resurgence was observed in the TPR trend, while the IR per 1,000 continued to decline.

There are instances where changepoints occurred earlier before the year of mass LLIN campaigns implemented. An example of this is the 2014 mass distribution campaign subgroup of the Nusa Tenggara (green lines), where both IR per 1,000 and TPR similarly showed earlier changepoints in 2013. The early changepoint detection in IR per 1,000 may have been influenced by the variability of cases detected at the end of 2013, while in TPR, the early drop was much clearer. Additionally, in the 2014 & 2017 campaigns subgroup of the Papua region, changepoints occurred earlier in both IR per 1,000 and TPR. However, for the context of this case, relatively large scale-ups already occurred in 2013.

Some interesting findings were also observed from mass campaigns implemented in the Maluku region. For example, in the 2014 & 2016 mass LLIN campaigns subgroup, both IR per 1,000 and TPR agreed that despite finding declines in the first campaign in 2014, both metrics did not show any changes during or after the implementation of the second campaign in 2016. These patterns were similar to the simulated model scenario example, where the second campaign's coverages were just enough to prevent a resurgence. Additionally, in the 2014 & 2017 mass campaigns subgroup, changepoint was not detected in 2014 for IR per 1,000, while it was detected for TPR.

Overall, the changepoints observed from the analysis of routine surveillance data show temporality and gradient changes which are largely qualitatively similar to the ones observed in the simulated model analysis, especially those occurring in the first campaigns for subgroups of multiple campaigns. Furthermore, these observations were observed largely consistently in two metrics representing the burden and transmission of malaria at the population level and across all subgroups and regions analysed, making a strong case for associations between mass LLIN campaigns and the declines of malaria burden and transmission.

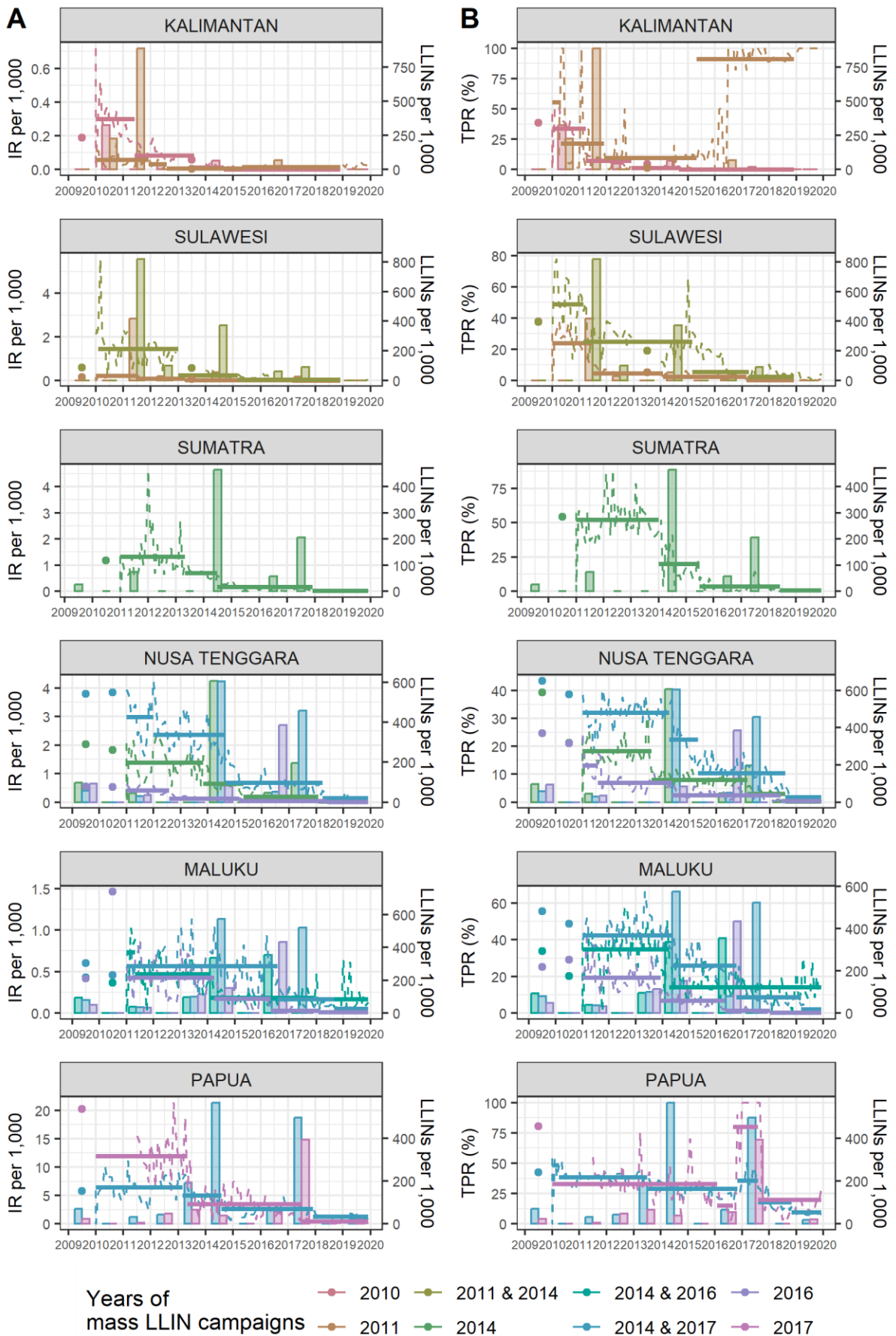


Figure 6.3. A) Implementations of changepoint algorithm to IR per 1,000 from routine data (dashed lines) in regions that conducted mass LLIN campaigns; B) Implementations of changepoint algorithm to TPR from routine data (dashed lines) in regions that conducted mass LLIN campaigns. In each region, the data were grouped by the years of mass LLIN campaigns. Number of LLIN distributed per 1,000 population each year are indicated by the barplots. Solid lines are the average values of the segments based on the changepoint estimates.

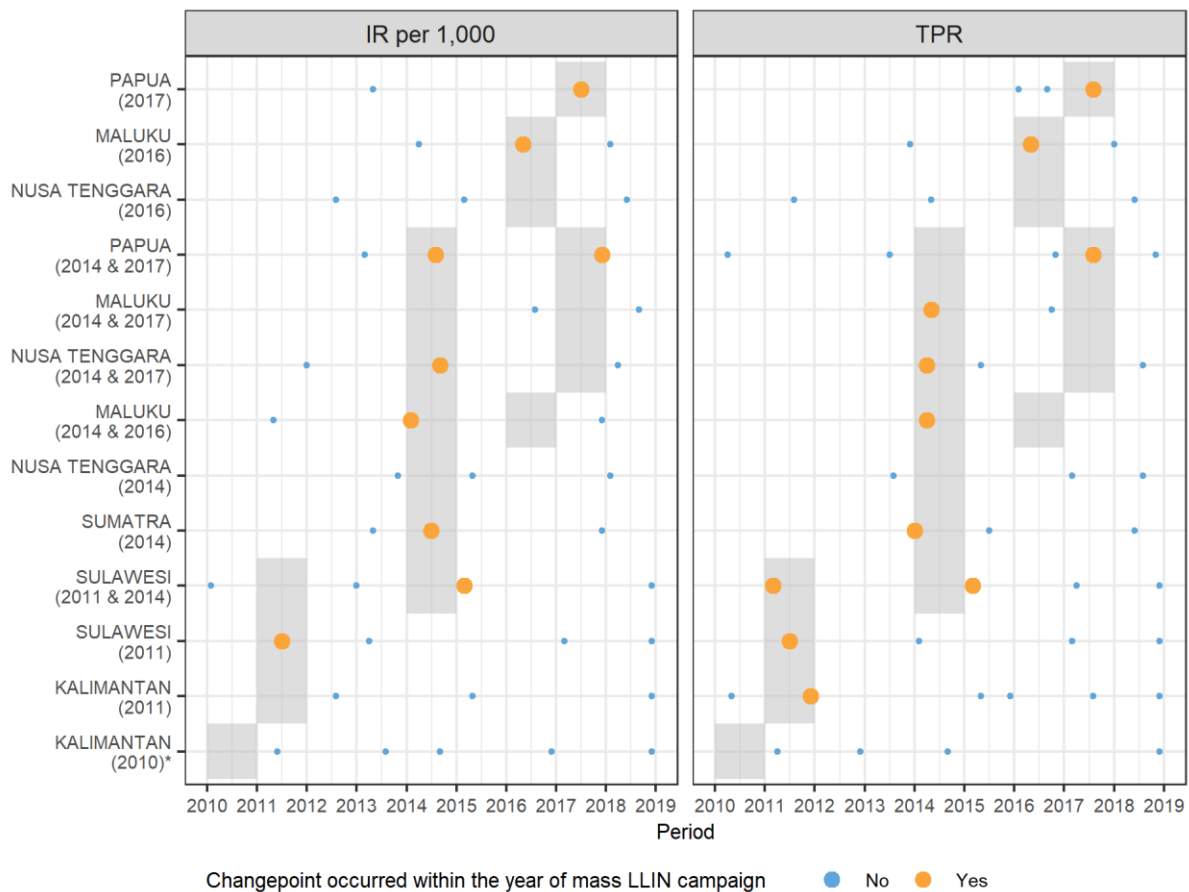


Figure 6.4. The changepoint timings for all regions grouped by the years of mass LLIN campaigns. Small blue points denote changepoints occurred outside the years of mass LLIN campaigns, while large orange points denote changepoints occurred during the years of mass LLIN campaigns in each group, which includes the first three-month period of the following year to account for any late distributions impact associated with the campaigns. Shaded grey areas denote the years of mass LLIN campaigns.

Table 6.4. Assessment of changes in incidence rate per 1,000 (IR per 1,000) between segments which changepoint coincide with LLIN mass distribution campaigns. Coverages at distribution refers to the operational term which were calculated assuming an average of 1.8 people covered by a single LLIN (World Health Organization, 2017).

Region	Years of distribution group (% coverages at distribution)	No of districts in this group	Year of first campaign	Temporality: Did the change happen contemporaneously to the distribution?	If not, is it reasonable to assume that it coincided with the distribution? Why?	Gradient: How big was the reduction relative to pre-LLIN?	Expected qualitative trends following first campaign (if LLIN main factor)	Were long term trends as expected?
Kalimantan	2010 (59%)	20	2010	No	Cannot conclude due to baseline year (2009) monthly data was not available.	-	Resurgence due to no subsequent mass campaign.	No. Declining trend continued.
	2011 (100%)	1	2011	Yes	-	45%	Resurgence due to no subsequent mass campaign.	No. Declining trend continued.
Sulawesi	2011 (75%)	27	2011	Yes	-	56%	Resurgence due to no subsequent mass campaign.	No. Declining trend continued.
	2011 (100%) & 2014 (67%)	2	2011	No	No. The closest changepoint detected in 2013.	-	Resurgence or no changes due to a lower intensity of the 2 nd campaign.	No. Continued decline observed despite lower intensity in the 2 nd campaign.
Sumatra	2014 (83%)	1	2014	Yes	-	77%	Resurgence due to no	No. Declining trend

							subsequent mass campaign.	continued.
Nusa Tenggara	2014 (100%)	4	2014	No	Yes. Changepoint occurred earlier in the previous year, likely due to the variability in the observed incidence, and maintained throughout the campaign year.	54%	Resurgence due to no subsequent mass campaign.	No. Declining trend continued.
	2014 (100%) & 2017 (82%)	11	2014	Yes	-	71%	Resurgence or no changes due to a lower intensity of the 2 nd campaign.	No. Continued decline observed despite lower intensity in the 2 nd campaign.
	2016 (70%)	7	2016	No	No. A slow declining trend is observed due to already low level of transmission.	-	Resurgence due to no subsequent mass campaign.	No. Declining trend continued.
Maluku	2014 (61%) & 2016 (63%)	1	2014	Yes	-	60%	Continued decline due to higher intensity of the 2 nd campaign.	Yes. Continued decline is observed.
	2014 (100%) & 2017 (93%)	10	2014	No	No. Qualitatively, data do not show any changes	-	Resurgence or no changes due to a lower	No. Continued decline observed

					before and after mass LLIN campaigns.		intensity of the 2 nd campaign.	despite lower intensity in the 2 nd campaign.
	2016 (78%)	5	2016	Yes	-	82%	Resurgence due to no subsequent mass campaign.	No. Declining trend continued.
Papua	2014 (100%) & 2017 (89%)	24	2014	Yes	-	48%	Resurgence or no changes due to a lower intensity of the 2 nd campaign.	No. Continued decline observed despite lower intensity in the 2 nd campaign.
	2017 (71%)	7	2017	Yes	-	87%	Resurgence due to no subsequent mass campaign.	Declining trend continued but resurgence might not yet be observed as the interval between the last campaign and the end of observation is just about 2 years.

Table 6.5. Assessment of changes in test positivity ratio (TPR) between segments which changepoint coincide with LLIN mass distribution campaigns. Coverages at distribution refers to the operational term which were calculated assuming an average of 1.8 people covered by a single LLIN (World Health Organization, 2017).

Region	Years of distribution group (% coverages at distribution)	No of districts in this group	Year of first campaign	<u>Temporality</u> : Did the change happen contemporaneously to the distribution?	If not, is it reasonable to assume that it coincided with the distribution? Why?	<u>Gradient</u> : How big was the reduction relative to pre-LLIN?	Expected qualitative trends following first campaign (if LLIN main factor)	Were long term trends as expected?
Kalimantan	2010 (59%)	20	2010	No	Cannot conclude due to baseline year (2009) monthly data was not available.	-	Resurgence due to no subsequent mass campaign.	No. Declining trend continued.
	2011 (100%)	1	2011	Yes	-	55%	Resurgence due to no subsequent mass campaign.	Yes. Resurgence occurred to a very high level (almost 100% TPR). Likely due to low testing.
Sulawesi	2011 (75%)	27	2011	Yes	-	80%	Resurgence due to no subsequent mass campaign.	No. Declining trend continued.
	2011 (100%) & 2014 (67%)	2	2011	Yes	-	49%	Resurgence or no changes due to a lower intensity of the	No. Continued decline observed despite lower intensity in the

							2 nd campaign.	2 nd campaign.
Sumatra	2014 (83%)	1	2014	Yes	-	62%	Resurgence due to no subsequent mass campaign.	No. Declining trend continued.
Nusa Tenggara	2014 (100%)	4	2014	No	Yes. Changepoint occurred earlier in the previous year and maintained throughout the campaign year.	56%	Resurgence due to no subsequent mass campaign.	No. Declining trend continued.
	2014 (100%) & 2017 (82%)	11	2014	Yes	-	30%	Resurgence or no changes due to a lower intensity of the 2 nd campaign.	No. Continued decline observed despite lower intensity in the 2 nd campaign.
	2016 (70%)	7	2016	No	No. A slow declining trend is observed due to already low level of transmission.	-	Resurgence due to no subsequent mass campaign.	No. Declining trend continued.
Maluku	2014 (61%) & 2016 (63%)	1	2014	Yes	-	60%	Continued decline due to higher intensity of the 2 nd campaign.	Yes. Continued decline is observed.
	2014 (100%) & 2017 (93%)	10	2014	Yes	-	39%	Resurgence or no changes due to a lower	No. Continued decline observed

							intensity of the 2 nd campaign.	despite lower intensity in the 2 nd campaign.
	2016 (78%)	5	2016	Yes	-	82%	Resurgence due to no subsequent mass campaign.	No. Declining trend continued.
Papua	2014 (100%) & 2017 (89%)	24	2014	No	Yes. Change point occurred earlier in the previous year and maintained throughout the campaign year.	25%	Resurgence or no changes due to a lower intensity of the 2 nd campaign.	No. Continued decline observed despite lower intensity in the 2 nd campaign.
	2017 (71%)	7	2017	Yes	-	75%	Resurgence due to no subsequent mass campaign.	Declining trend continued but resurgence might not yet be observed as the interval between the last campaign and the end of observation is just about 2 years.

Table 6.6. Summary of the frequencies of observed changepoints coinciding with the years of mass LLIN campaigns.

Region	First/second campaign	Metric	Total mass LLIN campaigns	Changepoints occurred during campaign years (as shown in Figure 6.4)	Proportion of campaigns with changepoints occurred during campaign years
PAPUA	First	API	2	2	100%
PAPUA	First	TPR	2	1	50%
PAPUA	Second	API	1	1	100%
PAPUA	Second	TPR	1	1	100%
MALUKU	First	API	3	2	67%
MALUKU	First	TPR	3	3	100%
MALUKU	Second	API	2	0	0%
MALUKU	Second	TPR	2	0	0%
NUSA TENGGARA	First	API	3	1	33%
NUSA TENGGARA	First	TPR	3	1	33%
NUSA TENGGARA	Second	API	1	0	0%
NUSA TENGGARA	Second	TPR	1	0	0%
SUMATRA	First	API	1	1	100%
SUMATRA	First	TPR	1	1	100%
SUMATRA	Second	API			-
SUMATRA	Second	TPR			-
SULAWESI	First	API	2	1	50%
SULAWESI	First	TPR	2	2	100%
SULAWESI	Second	API	1	1	100%
SULAWESI	Second	TPR	1	1	100%
KALIMANTAN	First	API	2	1	50%
KALIMANTAN	First	TPR	2	1	50%
KALIMANTAN	Second	API	-	-	-
KALIMANTAN	Second	TPR	-	-	-
Overall		API	18	10	56%
		TPR	18	11	61%

6.4 Discussions

This study used the plausibility design framework proposed by Yé et al. (Yé et al., 2017), which involved reviewing past studies and literature, analysing model simulations, and examining routine surveillance data to assess the plausibility that mass LLIN campaigns implemented throughout 2010-2019 across the country was the main driver of the decline of malaria incidence in Indonesia. This framework utilised the Bradford Hill causality criteria to assess all the evidence supporting the plausibility of the hypothesis. First, the model simulations demonstrated the plausible impact of different scenarios of LLIN mass campaigns on malaria incidence trajectories. These simulated impacts were also supported through various studies reviewed, where it has been established that LLIN is an effective intervention in reducing the malaria burden and transmission in the population. The analysis of routine surveillance data further revealed that the timing of mass LLIN campaigns largely coincided with the large reductions in IR per 1,000 and TPR across all regions in the country. Collectively, these findings strongly suggest that it is plausible to say that the scale-ups of LLIN through mass campaigns conducted in 2010-2019 were the main driver of the decline of malaria incidence in Indonesia.

The mechanism through which ITNs, including LLINs, prevent malaria transmission has been extensively studied (Griffin et al., 2010; Le Menach et al., 2007). Firstly, proper usage of ITN, especially during the evening sleeping time when most mosquitoes are active, creates physical barriers that prevent mosquito bites. This barrier interrupts the transmission of malaria parasites from the mosquito to humans and vice versa. Secondly, insecticides covering the nets could repel mosquitoes and kill them, reducing the density of mosquito vectors in the population and the probability of any mosquito surviving the extrinsic incubation period (EIP). This is expected to reduce the probability of infectious bites to community members at any time of the day or night. These biological properties of malaria transmission mechanisms are represented within the mechanistic model of malaria used for the modelling simulations in this study (Griffin et al., 2010, 2014). The model simulations showed how rapid scale-ups of LLIN usage in the form of mass distribution campaigns are expected to cause large declines in the clinical incidence of malaria. However, model simulations showed that a resurgence is expected if the LLIN usage coverage was not maintained through subsequent mass campaigns.

In addition to its biological plausibility, a review of relevant studies (as presented in **Table 6.6**) provides further evidence on the effectiveness of ITN usage in reducing malaria morbidity and transmission intensity at both the individual and population level, especially when compared to a non-usage of ITN (Bhatt et al., 2015; Henry et al., 2005; Marbiah et al., 1998; Nevill et al.,

1996; Pryce et al., 2018; Rowland et al., 1996; Smithuis et al., 2013; Sochantha et al., 2006). These studies provided evidence supporting the coherence (substantial literature and knowledge supporting the effectiveness of LLIN) and experiment (experimental studies supporting the associations between increased LLIN usage and decline in malaria incidence) of the Bradford Hill criteria. Moreover, two studies analysing routine surveillance data showed that in other countries, mass LLIN campaigns significantly reduced malaria incidence in the population, supporting the analogy criteria (Girond et al., 2018; Topazian et al., 2021). However, these studies also showed instances of the resurgence of malaria incidence within two years following the mass LLIN campaigns, highlighting the complexity of real-world scenarios that may not be fully captured in controlled experiments or trials (e.g., theoretically, LLIN works up to three years or 20 washes (UNICEF, 2022)). This resurgence can be influenced by various factors such as changes in mosquito behaviour (Thomsen et al., 2017), a decrease in bioefficacy of LLINs (Vinit et al., 2020), uncertainties around LLIN durability (Cleary et al., 2022), and differences in local factors, including terrain, remote access, knowledge about malaria transmission, and usage behaviour (including a potential gender bias) (Cleary et al., 2022). In Papua New Guinea, for instance, changes in the biting habits of *Plasmodium* vectors and shifts in vector species compositions in response to LLIN interventions have been observed, rendering vector control measures less effective (Cleary et al., 2022). Furthermore, these findings indicate how biological plausibility demonstrated by model simulations aligns with real-life observations. Up to the time of this study, I did not find either population-level experimental or quasi-experimental studies related to the impact of ITNs on malaria in Indonesia, making this study the first to evaluate the impact of ITNs in Indonesia at the population level.

Furthermore, the application of changepoint analysis to the routine surveillance data showed that changes in IR per 1,000 and TPR largely occurred during the year of mass LLIN campaigns, supporting the temporality criterion. The gradient criterion is also supported through the reductions in the average values of those metrics, ranging from 25% to 80% reductions, following the implementation of mass LLIN campaigns. These consistent findings were observed across all regions that specifically implemented mass LLIN distribution campaigns in the country, further strengthening the plausibility of the associations between the LLIN mass campaigns and the decline of malaria incidence in Indonesia.

The long-term patterns observed in the data largely deviate from the expected trajectories based on the assumption that LLIN mass campaigns are the main factor affecting the trajectories of the malaria metrics observed. Model simulations expected resurgences in malaria incidence to happen following mass campaigns when no subsequent campaigns were conducted. This discrepancy may be attributed to mass LLIN distribution campaign being just

one of several malaria interventions scaled up between 2010 and 2019. Other interventions, such as routine LLIN distribution in children and pregnant women, ACT treatment, indoor residual spraying, larval control, environmental management, laboratory confirmation, and screening in pregnant women, were also scaled up during the period, albeit to varying degrees across different geographic settings. While the incremental increases in coverage of these interventions may not have had an as large and immediate impact as the mass LLIN campaigns, sustained increases in their coverages may have contributed to changing the endemic equilibrium of malaria across those regions, thereby preventing the expected resurgences in malaria incidence when no further mass LLIN campaigns conducted. Model simulations of sustained increases in ACT coverage, for example, demonstrated the potential for sustained increases in intervention coverage in altering the malaria transmission dynamics.

Moreover, contrary to the expected trajectories based on model simulations, continued IR per 1,000 and TPR declines were observed in all regions that implemented multiple mass LLIN campaigns, even when the LLIN distribution coverage was lower during the follow-up campaign. In other studies that utilised longitudinal routine surveillance data (Girond et al., 2018; Topazian et al., 2021), resurgences in malaria cases were observed at least two years after implementing mass distribution campaigns, especially in high-transmission settings. Other observational studies (Gnanguenon et al., 2014; Lorenz et al., 2020) also suggest that resurgences in malaria cases are likely to happen due to the waning protective effectiveness of the LLIN and their use over time. These results could suggest that campaigns had become better targeted to those most in need during the follow-up campaigns. Furthermore, they could be a result of the offsetting effect of other interventions, such as improved surveillance systems or the scale-up of use of ACTs, or the influence of other factors, such as improved housing or changes in climate, that may have reduced the intrinsic malaria receptivity in these regions.

It is also worth highlighting how the 2014 & 2017 mass campaign subgroup from the Papua region, comprising districts with the highest malaria endemicity in the country that received most of the LLINs distributed across the country, was the subgroup with the lowest relative reductions with respect to their IR per 1,000 and TPR following the initial mass LLIN campaigns compared to other mass campaign subgroups. Moreover, even a changepoint analysis for the TPR detected a resurgence after a small reduction following the mass LLIN distribution campaigns in 2014. These highlight some interesting patterns that are worth further investigation.

Finally, it is important to acknowledge that the changepoint analysis utilised in this study has limitations when evaluating the impact of malaria interventions using routine surveillance data. Inconsistent and incomplete reporting of malaria incidence can introduce biases into the analysis framework. Despite those limitations, contextual interpretation of the findings can help

mitigate the impact of these biases. The plausibility design framework based on the Bradford Hill causality criteria is useful for providing contextual interpretations to overcome biases that may come from routine data. Collectively, the evidence presented in this study showed that it is plausible to conclude that mass LLIN campaigns conducted over the 2010-2019 decade were the main driver of the decline in malaria transmission across Indonesia.

6.5 Conclusions

In this chapter, I utilised the plausibility design framework to assess the evidence for mass LLIN campaigns being the main driver of declines in malaria incidence in Indonesia over the 2010-2019 period. By collectively assessing the findings and evidence from the literature review, model simulations, and analysis of routine surveillance data using the Bradford Hill causality criteria, I found that it is plausible to conclude that LLIN mass distribution campaigns conducted across the country in 2010-2019 were the main cause of declines in malaria incidence in Indonesia. This study also suggests that scale-ups of other interventions may have further lowered the malaria endemic equilibrium across the country, preventing the expected subsequent resurgences if no subsequent mass LLIN campaigns are conducted, or the subsequent distribution campaign coverages are lower than the first ones. Following up on this, **Chapter 7** is a further investigation, utilising higher resolution data, regarding malaria trends and intervention impacts in the high-endemic region of Papua.

Chapter 7: Qualitative explorations on the impact of mass LLINs campaigns on *Plasmodium falciparum* malaria incidence in Papua using mathematical models calibrated to routine malaria surveillance data

In the previous chapters, I have shown how the scale-up of interventions, especially the distribution of long-lasting insecticide-treated nets (LLINs), reduced malaria transmission in the region of Papua. However, despite following a comparable approach to other regions of sustained transmission, including multiple LLIN campaign cycles, apparent progress towards malaria elimination has been comparatively slow: in 2010, cases in the region represented approximately 40% of all cases in Indonesia; by 2019, this proportion had risen to over 80%.

This chapter provides a higher-resolution analysis aiming to better understand the potential determinants of progress and intervention impact in a region characterised by a high degree of heterogeneity in a wide range of factors relevant to malaria receptivity. I begin by analysing sub-regional disparities in surveillance effort and LLIN distribution, using established methods attempting to, respectively, quantify how these relate to the likely underlying trends in cases and effective coverage of LLINs over time in each district. I then calibrate an established model of *Plasmodium falciparum* malaria transmission and burden, developed at Imperial College London, to these estimates of scale-up and the most recent case trends in an attempt to estimate the baseline transmission intensity in the absence of interventions. Moving backwards in time, I then compare case trends reconstructed by the model to those in the data. In doing so, I aim to assess the extent to which differences in surveillance strength, intervention uptake, and baseline endemicity provide a coherent explanation for the divergent reported case trends across different districts of Papua in the post-LLIN-scale-up era.

7.1 Introductions

7.1.1 Background

Papua is the easternmost region of Indonesia, located in the western half of the second largest island in the world, New Guinea, with a total area of around 442,000 km². The region comprises two provinces, Papua Barat (West Papua) and Papua (themselves comprising of thirteen and twenty-nine districts respectively), where malaria is highly endemic. For clarity, whenever I mention ‘Papua’, it refers to the Papua region. Therefore, I refer to the Papua province as

'Papua province' for the rest of the thesis. The Papua province shares a 750 km land border with Papua New Guinea (PNG). The region has a wide range of ecological features, from a coastal range with low hills, swamps, and marshes to mountainous areas as high as 5,000 meters (Church et al., 1995). The climate is characterised by perennial rainfall except in the Merauke district of the south coast, where a distinct dry season can be found between May and October (S. Gunawan, 1985). The yearly average temperature of the region ranges from 29°C to 31.8°C. In districts located in the mountainous areas, the average temperature could reach 14.5°C (Geost, 2019).

Malaria transmission settings in Papua range from perennial transmission in the meso- to holoendemic in the coastal and lowland areas to the more unstable, seasonal, and potentially epidemic transmission in the highlands (S. Gunawan, 1985; Karyana et al., 2008; V. H. Lee et al., 1980). However, increased transmission of stable malaria had been observed in the highlands of Papua with extensive constructions of drainage ditches for more modern social housing, serving as additional vector breeding sites, suspected as the cause of the upsurge (Anthony et al., 1992). Four malaria parasites known to infect humans, *P. falciparum*, *P. vivax*, *P. malariae* and *P. ovale*, are endemic in Papua, with *P. falciparum* and *P. vivax* accounting for the majority of infections (Fadilah et al., 2022). Children bear the highest burden in terms of cases in the population, especially those under five years old (Fadilah et al., 2022). In early infancy, *P. vivax* becomes the major cause of morbidity, with overall infections peaking in the younger age groups in children compared to *P. falciparum* (Douglas et al., 2020; Karyana et al., 2008; Poespoprodjo et al., 2009). Malaria also contributes significantly to maternal morbidity and mortality in the region (Poespoprodjo et al., 2008).

Before the introduction of vector control using DDT spraying, malaria control in Papua during the Dutch colonial era relied on vector controls through the oiling of breeding sites and drainage works to suffocate larval stage mosquitoes and chemoprophylaxis to the non-indigenous population (S. Gunawan, 1985). In the late 1950s, DDT spraying was implemented twice a year as the main vector control intervention alongside mass drug administrations (MDAs) with chloroquine and pyrimethamine. This combination of interventions managed to interrupt transmission in some areas, but in others, the interruption was without lasting effect (S. Gunawan, 1985). The malaria control program in Papua deteriorated in the 1960s due to the country's financial and political situation. However, in the 1970s, when the political situation was stabilised, hyperinflation was controlled, and a realistic development plan was prepared, the malaria control program was reactivated. The focus of the malaria control program during 1970-1980 was to control malaria in the areas of socio-economic importance in Papua using a combination of vector control through DDT spraying and larviciding and case management (S. Gunawan, 1985).

The transmigration program began in the 1980s, bringing an influx of non-immune people from relatively low-endemic regions in Java, Bali, and Lombok to Papua (Church et al., 1995). Forest cutting to provide housing for transmigrants resulted in a high increase of breeding sites for malaria vectors, providing an ideal condition for malaria epidemics in transmigrant communities (Church et al., 1995). In the 1990s, insecticide-treated nets (ITNs) were distributed, and housing walls were treated in the transmigrant areas (Church et al., 1995). Furthermore, the emergence of multidrug-resistant parasites in the region led to the introduction of artemisinin-based combination therapy using dihydroartemisinin-piperaquine (DHP) as the first-line treatment for malaria cases in the mid-2000s (Karyana et al., 2008; Poespoprodjo et al., 2008; Ratcliff et al., 2007; Tjitra et al., 2008).

In 2009, the Indonesian government initiated an ambitious campaign to eliminate malaria by 2030, with the Papua region targeted as the last region to eliminate malaria in the country (Departemen Kesehatan, 2009). The new strategy, based on malaria endemicity, gave decentralised authority to tailor malaria control at the subnational level relying on improvements in surveillance, case management, and vector controls (Sitohang et al., 2018). As a result, Papua as a high endemic region was classified into the acceleration phase with improved diagnostics and case management, LLIN mass distribution campaigns, and targeted Indoor Residual Spraying (IRS) as its main interventions (Ministry of Health of the Republic of Indonesia, 2014).

It has been over a decade since the Indonesian government proclaimed the malaria elimination commitment. However, studies that were done to evaluate policy and the impact of scale-ups of interventions in the Papua region are either qualitative (Directorate General of Disease and Prevention, 2020; Ministry of Health of the Republic of Indonesia, 2014; Mobilala et al., 2019; Pasik & Darmawan, 2019) or only done at the province-level (Supriyanto & Bachtiar, 2019). Therefore, quantitative analysis of the intervention impacts that were conducted at a higher resolution (i.e., district level) is needed to measure and evaluate control programs objectively in the area with heterogeneous transmission settings such as Papua (Ashton et al., 2020).

Figure 7.1 shows the province-level and region-level trajectories of Annual Parasite Incidence (API) per 1,000 of all malaria species, API per 1,000 of *P. falciparum* malaria (PfAPI per 1,000), test positivity ratio (TPR), and annual blood examination rate (ABER) of Papua Barat and Papua provinces, comprising the Papua region, and the Papua region as a whole. In 2012, the year prior to the first LLIN campaign, API across the two provinces was nearly identical, though a higher proportion of cases in Papua were *P. falciparum*. Similarities in API were also driven partly by disparities in surveillance, with higher TPR in Papua being offset by higher testing rates (as measured by ABER) in Papua Barat. During the 2012-2014 'intervention scale-up' stage, API declined at a similar rate in each province. Although these trends are likely to have

been influenced by concomitant declines in testing rates across the region, reductions in TPR support an underlying impact upon malaria across the region. However, during the subsequent ‘maintenance’ stage in 2015-2020, the two provinces began to follow different paths – with Papua Barat province showing relatively continuous progress towards elimination, while Papua province, by 2017, had experienced a resurgence in both API and TPR. From 2017 onwards, testing rates across the region have substantially improved, particularly in Papua province, which now has the highest ABER of the two provinces. During this period, in which a second LLIN campaign was completed, API remained high in Papua province, though TPR in the province declined. Meanwhile, both API and TPR continued to decline in West Papua.

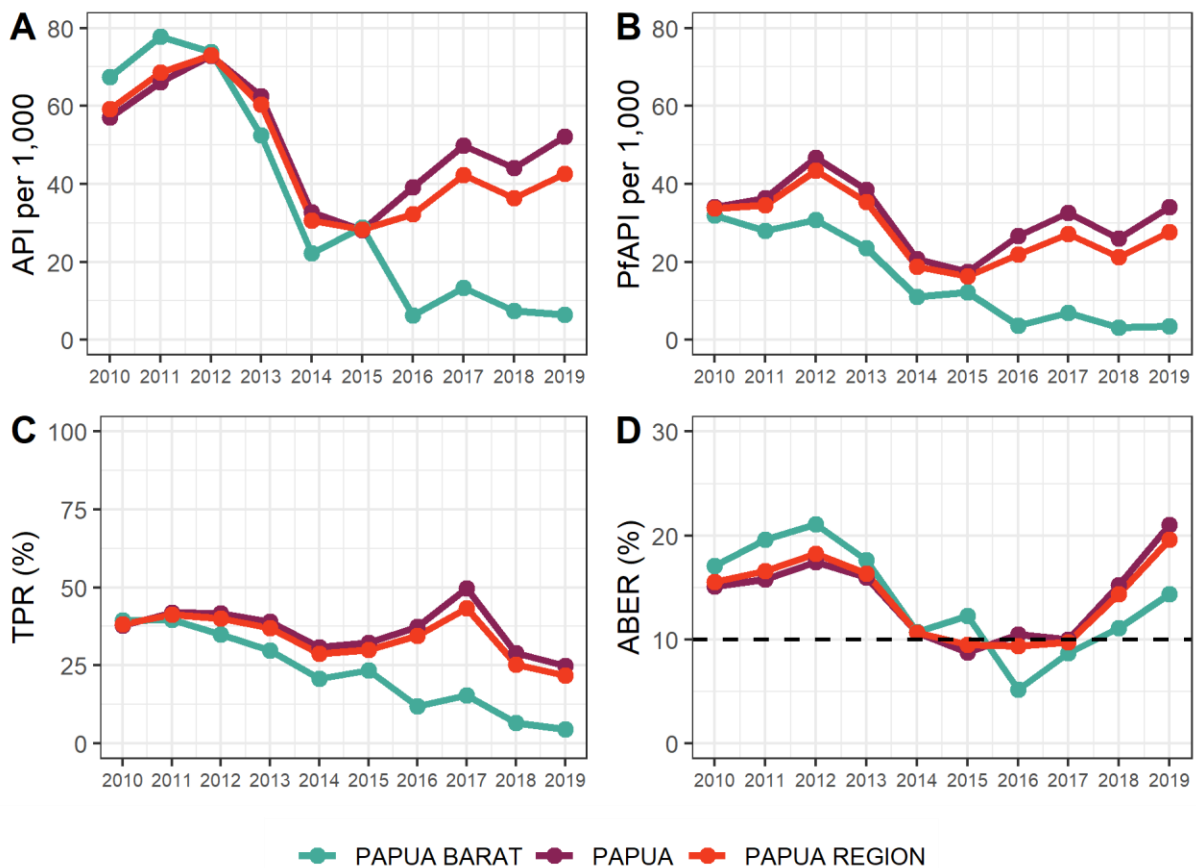


Figure 7.1. Province-level and region-level trajectories of some malaria metrics from routine surveillance data. A) annual parasite incidence (API) per 1,000, B) *P. falciparum* annual parasite incidence (PfAPI) per 1,000, C) test positivity ratio (TPR), and D) annual blood examination rate (ABER).

These differences underscore the value of analysing malaria dynamics at a higher spatial resolution than the region level. In the Papua region, given the high diversity of transmission intensity within its provinces (not at least due to the role of altitude), I conducted an analysis at the district level to investigate the potential drivers of the observed case trend differences between the provinces in the region. These drivers can broadly be categorised into three groups: 1) differences in reporting systems; 2) operational constraints that affect the uptake of

intervention measures (e.g., treatment-seeking behaviour, LLINs distribution levels and their subsequent usage in the population); 3) technical constraints that govern the impact of intervention measures when taken-up at a particular level (e.g., the inherent endemicity of a setting, vector bionomics, insecticide/drug resistance).

In this chapter, I examined differences in key variables at the district level that broadly reflected these hypotheses and attempted to incorporate these differences within a modelling framework to assess whether they provide a consistent explanation for differences in the reported case trajectories across the region, particularly during the 2015-2020 ‘maintenance’ stage. Through this analysis, I aimed to provide a better understanding of the malaria case trajectories in the Papua region following the scale-up of interventions and the sub-region heterogeneity present, which will ultimately provide insights into future effective intervention strategies for the region.

7.1.2 Aims

In this chapter, the analyses were focused on the *P. falciparum* malaria case trajectory after the reimplementation of LLIN campaigns in Papua in the second half of the 2010-2019 decade. The aims of the analysis are to:

1. Assess malaria reporting systems in the Papua region and account for their effects using a well-established case-adjustment methodology developed by WHO.
2. Conduct an in-depth analysis of district-level LLIN distribution data and how much they cohere with population usage survey data.
3. Calibrate an established model of the relationship between malaria endemicity and intervention impacts, parameterised using district-level vector bionomics and abundance, as well as the WHO-adjusted malaria cases and intervention scale-ups outlined above.
4. Assess whether the model provides a consistent explanation for the observed differences in the malaria case trajectories across the Papua region during the 2015-2020 ‘maintenance’ stage.

7.2 Data and methods

7.2.1 Data

7.2.1.1 Routine surveillance data of malaria in Papua, Indonesia

The complete list of all districts within the Papua region and their geographical locations can be seen in **Table S7.1** and **Figure S7.1**, respectively. The routine surveillance data from the Indonesia National Malaria Control Program (NMCP) comprise monthly malaria-related data at the district level across the country. The data contains:

- malaria incidence by age groups and sex,
- malaria incidence by parasite species,
- number of malaria tests conducted (by microscopy or rapid diagnostic test/RDT), and
- the annual district and province reporting completeness.

Reporting completeness is defined as the proportion of primary health centres (Pusat Kesehatan Masyarakat or Puskesmas) within a district or province that reported their routine malaria surveillance data to the district health agency. District-level reporting completeness in Papua is only available for 2018 and 2019. For province-level reporting completeness, data are available for 2011, 2012, 2013, 2014, 2015, 2018 and 2019 for Papua Barat province, and 2012, 2018 and 2019 for Papua province. For the imputations of the district-level reporting completeness from 2010 to 2017, there are two steps. First, reasonable imputations based on the ratio of reported malaria tests were done to impute missing data on province-level reporting completeness (**Figure S7.2**). Then, imputations of district-level reporting completeness for years before 2018 were done, accounting for province-level reporting completeness, the number of primary health centres within each district, and average district contribution to the overall province-level reporting in 2018 and 2019. The district-level reporting completeness, including the imputed data for 2010-2017, is shown in **Figure S7.3**. The details of these steps are available in the **Appendix**.

7.2.1.2 LLINs distributions data in Papua, Indonesia

The LLINs distributions data comprise the number of LLINs distributed each year at the district level. The distribution data do not mention the type or brand of LLINs distributed. However, they detail whether sources of procurement funding came from the government's budget (Anggaran Pendapatan dan Belanja Negara/APBN) or the Global Fund. For the context of the analysis, I assumed that the type of the LLINs distributed that were procured using either funding source were similar. Hence, the total number of LLINs distributed each year within a district is the total number of LLINs procured (and distributed) from either source of funding mechanisms.

7.2.1.3 LLINs usage surveys data

The district-level LLINs usage proportions were calculated from the data gathered in 2018 Basic Health Research (Riset Kesehatan Dasar/Riskesdas) in Indonesia (Badan Penelitian dan Pengembangan Kesehatan, 2019a, 2019b).

7.2.1.4 Treatment-seeking behaviour data

The province-level treatment-seeking proportions at public and private health centres or not seeking treatment at all were estimated using the data from Demographic Health Surveys in 2012 and 2017 (National Population and Family Planning Board et al., 2018; Statistics

Indonesia - Badan Pusat Statistik - BPS et al., 2013; Watson, FitzJohn, et al., 2019). The surveys asked specific questions about whether a child had a fever or cough or not within a month before the survey. Then those children who had fever or cough were asked whether they sought treatment at a public health service or private health service or did not seek treatment at all. The proportions of children with fever or cough who sought treatment from the DHS surveys were used as a proxy of the population's treatment-seeking behaviour. **Table S7.2** shows the province-level calculated treatment-seeking behaviours for the two provinces in the Papua region in 2012 and 2017. A few other studies also assess the treatment-seeking behaviour, specifically of those who had malaria in districts in the Papua region of Indonesia (Devine et al., 2018; Karyana et al., 2016; Kenangalem et al., 2019). The proportion of people who sought treatment for malaria from those studies was also summarised in **Table S7.2**. Then consensus values for the population treatment-seeking behaviour in 2012 and 2017, considering the DHS survey results and those additional studies, were shown in **Table S7.3**.

Additionally, for the purpose of malaria incidence adjustment, I assumed that the treatment-seeking behaviours for 2010-2011 and 2018-2019 were similar to those in 2012 and 2017, respectively. For the years between 2012-2017, a linear interpolation was used to estimate the treatment-seeking behaviour.

7.2.1.5 District-level population data

As previous two chapters, I used the estimated district-level population data using linear interpolation between two censuses (in 2010 and 2020) as previous two chapters.

7.2.1.6 District-level proportion of the three most dominant *Anopheles* vectors in Papua

The district-level proportions of the three most dominant *Anopheles* vectors in Papua were derived from the Malaria Atlas Project rasterised estimates of species abundance (D. Pfeffer et al., 2020; D. A. Pfeffer et al., 2018):

1. For each dominant *Anopheles* species in Papua, *Anopheles farauti*, *Anopheles punctulatus*, and *Anopheles koliensis*, the district-level total species abundance was calculated by a summation of all pixel values that fall within the district polygon.
2. The total abundance of the three species was calculated for each district.
3. The proportion of each species in each district was calculated by dividing the species-specific abundance by the total species abundance.

7.2.1.7 Elevation data

The elevation data were downloaded using the `elevateR` package in R (Hollister et al., 2022), which give access to the elevation data from the Amazon Web Services Open Data Terrain Tiles. Then, for each district, the average district elevation (metres above the sea level, *m*

a.s./.) was estimated by calculating the average value of all elevation raster pixels that fall within each district's polygon.

7.2.2 Methods

7.2.2.1 Malaria incidence adjustment using WHO adjustment method

WHO used various methods to adjust the malaria incidence reported by every country in their World Malaria Report (World Health Organization, 2021b). The adjustment of incidence was aimed at estimating the actual burden of malaria in a country after accounting for reporting completeness of the country's routine surveillance system and the population's treatment-seeking behaviour. As a country outside the WHO African region, WHO uses the following formula to estimate the adjusted number of malaria cases in Indonesia:

$$T = \frac{(a + (c \times e))}{d} \times \left(1 + \frac{f}{g} + \frac{1 - g - f}{2g}\right)$$

where:

- a represents malaria cases confirmed and reported in the public sector
- b shows the suspected malaria cases tested
- c indicates the presumed cases which were not tested but treated as malaria (the value is zero for this analysis context)
- d is reporting completeness
- e is tests positivity ratio (malaria positive fraction) = a/b
- f is the fraction of the population who are seeking treatment in the private sector
- g is the fraction of the population who are seeking treatment in the public sector
- The fraction of the population not seeking treatment is calculated as: $(1 - g - f)$

The malaria incidence adjustments were conducted for malaria incidence of all species and malaria incidence of *P. falciparum* (which is defined as the total incidence of *P. falciparum* and mixed infections of *P. falciparum* and *P. vivax*). The adjustments were made for all districts, accounting for the district-level reporting completeness and the province-level treatment-seeking behaviour. Therefore, I assumed that their respective province's values represented the treatment-seeking behaviours of all districts in a province.

7.2.2.2 Converting LLINs distribution numbers to population access and usage

In this chapter, the analysis will go beyond the coverage of the LLINs distribution, as discussed in the previous chapter. There is additional terminology and metrics related to LLINs distributions and usages in this chapter. *Coverage* refers to the operational metric for procurement purposes which account for an overall ratio of one LLIN for every 1.8 persons on average (World Health Organization, 2017). *Access* is defined as what proportion of the

population could sleep under a net assuming two people per net (Bertozzi-Villa et al., 2021). Finally, *usage* is defined as the proportion of population does sleep under a net (Bertozzi-Villa et al., 2021), typically measured according to the proportion of people who slept under a net the previous night within surveys.

In their paper, Bertozzi-Villa et al. modelled the relationship between net per capita (the number of bednets distributed divided by the total population of an area where the bednets were distributed) and access using the data from 40 highest-burden countries in Africa (Bertozzi-Villa et al., 2021). The modelled relationship can be seen in **Figure S7.4**. I used the modelled relationship between net per capita and access to calculate district-level access of LLINs for each year of LLINs distribution. After calculating the access, the population usage proportion of LLINs was modelled using an exponential model that assumed a half-life of retainment of LLINs of 5 years. In this exponential model, bednets will be randomly removed in each timestep with a rate of:

$$1 - \exp\left(-\frac{1}{\text{retention}}\right)$$

However, the modelled population-level usage over time sometimes did not match with the proportion of people who slept under a bednet from surveys done in 2018 (Badan Penelitian dan Pengembangan Kesehatan, 2019a, 2019b). I then define a district-level access-to-usage coefficient, τ , representing the multiplier of projected access levels within the model needed to achieve the LLIN usage levels within the survey in mid-2018.

7.2.2.3 Setting up model parameters for the Imperial *P. falciparum* malaria model

7.2.2.3.1 Mosquito parameters

Mosquito bionomics parameters were set up for each of *An. farauti*, *An. punctulatus*, and *An. koliensis*. The adult mosquito bionomics parameters for each species and their sources are shown in **Table S7.4**. As the model input, the proportions of the presence of each mosquito within each district were also defined. The estimated proportions for each species based on the MAP estimated species abundance are shown in **Table S7.5**.

7.2.2.3.2 Treatment parameters

Dihydroartemisinin-Piperaquine (DHP) is the main artemisinin-based combination therapy (ACT) for malaria in Indonesia. Using the modelled efficacy parameters of the drug embedded within the Imperial malaria model, the effect of DHP usage as the primary malaria treatment on malaria transmission and burden was accounted for in the model. The modelled effect would also account for the proportion of clinical cases seeking malaria treatment. For districts in Papua Barat and Papua provinces, the proportion of clinical malaria cases seeking treatment and treated with DHP changed its value three times in 2005, 2012, and 2017. The values for

each year in Papua Barat province are 45%, 50%, and 70%. At the same time, the values for Papua province are 45%, 65%, and 45%.

7.2.2.3.3 Bednet parameters

The bednet parameter inputs modified the number of bednets ‘distributed’ at a specific time. For all the yearly distributions, I assumed that the distributions happened in the middle of the year, except for 2017, where the campaigns occurred later in the year (October). The number of new nets that reach, and are used, by their intended recipients during each campaign in each district is calculated by calculating per-capita, which is then passed through the distribution-to-access formula of Bertozzi-Villa et al. and scaled by the district-level access-to-usage τ . The model assumes that the nets are received overnight and immediately used by the recipients, which are assigned randomly. A new net received replaces any older net the individual would otherwise be currently using.

7.2.2.3.4 Rest of model parameters

The rest of the model parameters have similar values to those described in this thesis’ Chapter 1 supplementary materials in **the Appendix**.

7.2.2.4 District-level baseline EIR calibrations to malaria incidence data

For each district with its unique model parameters input, ten years of daily clinical *P. falciparum* malaria incidence (2010-2019) were simulated based on 100 initial *P. falciparum* EIR (PfEIR) values. The distribution of the 100 initial PfEIR values used for model simulations is shown in **Figure S7.5**. Then, the yearly clinical *P. falciparum* malaria incidence per 1,000 population (modelled PfAPI per 1,000) for each PfEIR value in each district was calculated. A population size of 100,000 people was used as the representative population size for model simulations to minimise the stochastic effect of the simulations, which may lead to ‘elimination’ in some incidence simulations when simulated using a smaller population size.

The ‘best fit’ PfEIR for each district was chosen by finding the PfEIR value, which minimised the squared differences between the modelled PfAPI per 1,000 and the WHO-adjusted PfAPI per 1,000 in 2019. The year 2019 was chosen for the calibration both on the grounds of recency and as the year in which testing rates at the province level were the highest within the data. Three districts did not have reported malaria data in the surveillance data in 2019, Pegunungan Arfak of Papua Barat province, and Tolikara and Dogiyai of Papua province. For those three districts, the ‘best fit’ PfEIR was chosen after fitting the modelled PfAPI per 1,000 to the adjusted PfAPI per 1,000 in 2018.

The concordance between the model trajectory and the reported malaria data was evaluated in the ‘maintenance’ period between 2015 and 2019, the period of key interest where reported

API trends diverge between the two provinces, in particular whether the model trajectory and WHO-adjusted trends were in agreement as to the size and scale of any resurgence in cases relative to the incidence in 2014, immediately following the first mass LLIN campaign.

7.2.2.5 Assessing the province-level impact of LLIN distributions

The province-level impact is assessed by measuring the total reduction in *P. falciparum* incidence, comparing the yearly incidence to a baseline value that serves as a 'counterfactual' assuming no distribution of LLINs. The baseline value, representing 'pre-LLIN campaign' stage, is determined as the maximum value of PfAPI per 1,000 between 2010 and 2012. Then, the PfAPI per 1,000 differences are calculated for each year. If the maximum value occurred in 2011 or 2012, PfAPI per 1,000 differences for previous years are assumed to be 0. To determine the absolute incidence reduction for each year, the PfAPI per 1,000 differences are multiplied by the total population of that year. Cumulative incidence reductions are then calculated as the sum of the absolute impact of LLIN distributions over time. The relative incidence reductions per distributed LLIN are calculated by dividing the cumulative incidence reductions by the cumulative number of LLINs distributed. These impacts are calculated using the reported data and modelled estimates.

7.3 Results

7.3.1 Reporting systems assessment using WHO case-adjustment formula

Figure 7.2A show a comparison of temporal patterns for the province-level PfAPI per 1,000 between the reported data and the WHO-adjusted values from 2010 to 2019. In Papua Barat province, the yearly ratios between the WHO-adjusted values and the reported data were higher during the 'pre-LLIN' and 'intervention scale-up' stages (2010-2014), with an average ratio of 3, and the gap between the adjusted values and the reported data became smaller during the 'maintenance' stage (2015-2019), with an average ratio of 2.2 and the smallest ratio of 1.5 in 2019. Similar patterns can also be seen in Papua province, where the gap between the WHO-adjusted values and the reported data became smaller, in general, during the 'maintenance' stage, except in 2017, when the ratio between the WHO-adjusted values and the reported data was 9.7. Excluding the 2017 anomaly, the ratio went down from 4.6 before the 'maintenance' stage to 3.7 during the 'maintenance' stage, which is still higher than the ratio observed in Papua Barat province.

Figures 7.2B, 7.2C, and 7.2D illustrate the district-level maps of reported PfAPI per 1,000, WHO-adjusted PfAPI per 1,000, and their ratios based on 2019 data wherever available. These maps present the heterogeneous malaria endemicity across the districts in the Papua region and highlight the discrepancies between the reported data and the WHO-adjusted values, which vary across districts. In Papua Barat province, the ratio ranged from 1.25 (Fakfak,

Kaimana, Sorong Selatan, and Manokwari Selatan) to 2.7 (Kota Sorong) in 2019. While in Papua province, the ratio ranged from 1.83 (Intan Jaya, Merauke, Mappi, Boven Digoel, Jayapura, Supiori, and Mimika) to 91.7 (Yahukimo) in 2019. However, lower-lying districts in Papua province remain those with highest endemicity both pre- and post-adjustment, with districts with higher altitude and in Papua Barat typically at lower levels.

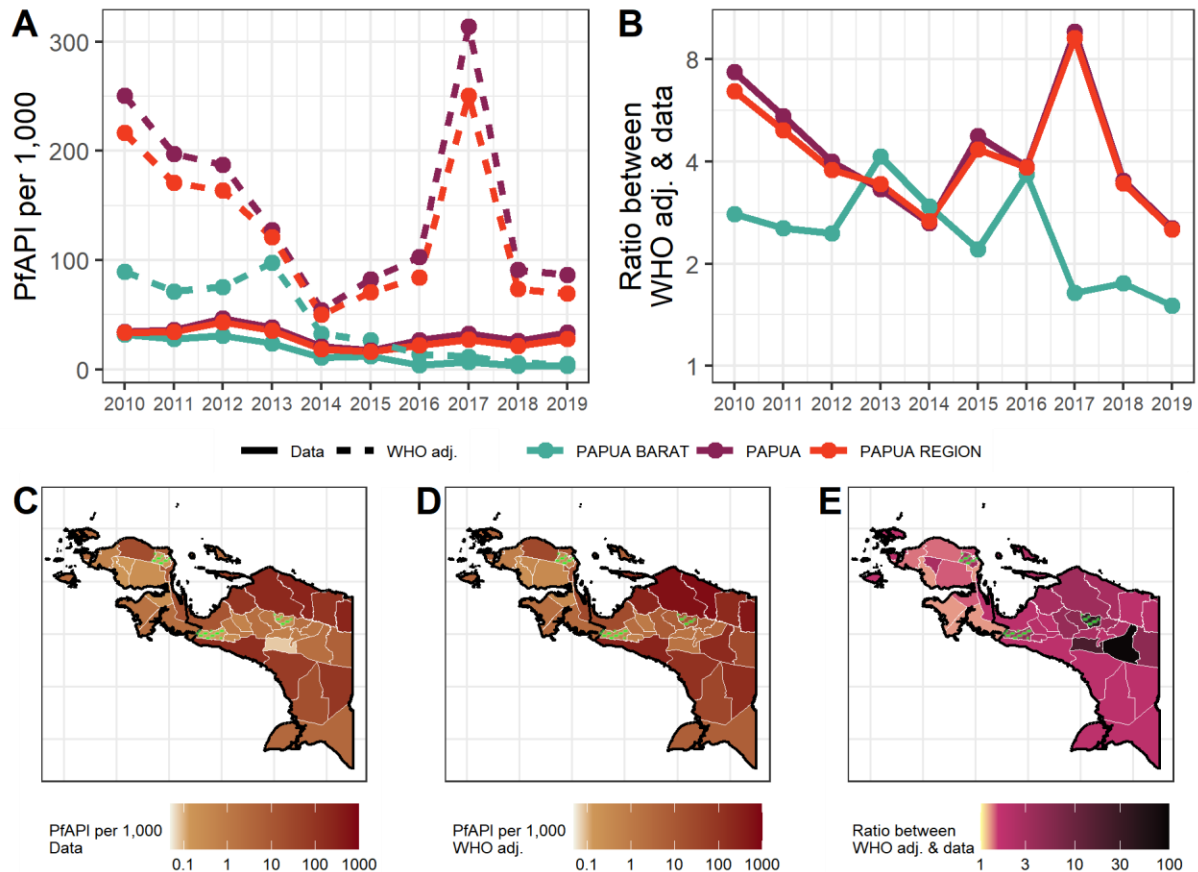


Figure 7.2. Comparisons between province- and district-level reported PfAPI per 1,000 and WHO-adjusted PfAPI per 1,000. A) Yearly province-level PfAPI per 1,000 comparison between reported data and WHO-adjusted values; C) Province-level ratio between WHO-adjusted and reported PfAPI per 1,000 (y-axis at a base-2 log-scale); C) District-level reported PfAPI per 1,000 (data); D) District-level WHO-adjusted PfAPI per 1000; and E) The ratio between WHO-adjusted and reported PfAPI per 1,000. All maps showing 2019 data (and their adjusted values and ratios) except for three districts (Pegunungan Arfak, Tolikara, and Dogiyai) where the polygons were shaded with green lines.

7.3.2 LLINs distributions and usage patterns in Papua

Heatmaps of the district-level yearly LLINs distributed per capita in Papua Barat and Papua provinces from 2009 to 2019 are shown in **Figures 7.3A**. The heatmaps highlight the large-scale LLINs distribution during the 'intervention scale-up' stage in 2012-2014, followed by mass distribution campaigns in 2017, except in Waropen and Paniai, which conducted their LLIN mass distribution campaigns in 2016. **Figure 7.3B** shows the map of the access to usage coefficient across districts in Papua. A smaller coefficient value indicates a larger gap between the LLINs distributed and their actual usage in the population, while a high coefficient value

(with a maximum of 100%) suggests that the distributed LLINs were highly utilised by the population. Overall, LLIN utilisation was higher in Papua Barat province than in Papua province. However, districts with very high access to usage coefficients were also found in the mountainous central region of Papua province.

Figure 7.3C shows the conversion of the distribution data into yearly coverages as the input for the mathematical model of malaria, summarised at the province level. LLIN distribution coverages, coverages after fitting, and usage over time were higher in Papua Barat province than in Papua province. **Figure S7.6** presents the more detailed district-level LLIN usage model fittings to the survey data for Papua Barat and Papua provinces, respectively (**Figures S7.7** and **S7.8** show the district-level equivalent of **Figure 7.3C**). The estimates of usage trends throughout 2010-2019 would suggest substantial LLIN usage declines throughout the first stage of the 2015-2019 maintenance period. However, subsequent LLIN top-ups increased estimated usage once again to similar levels to those achieved following the first 2012-2014 LLIN scale-up period.

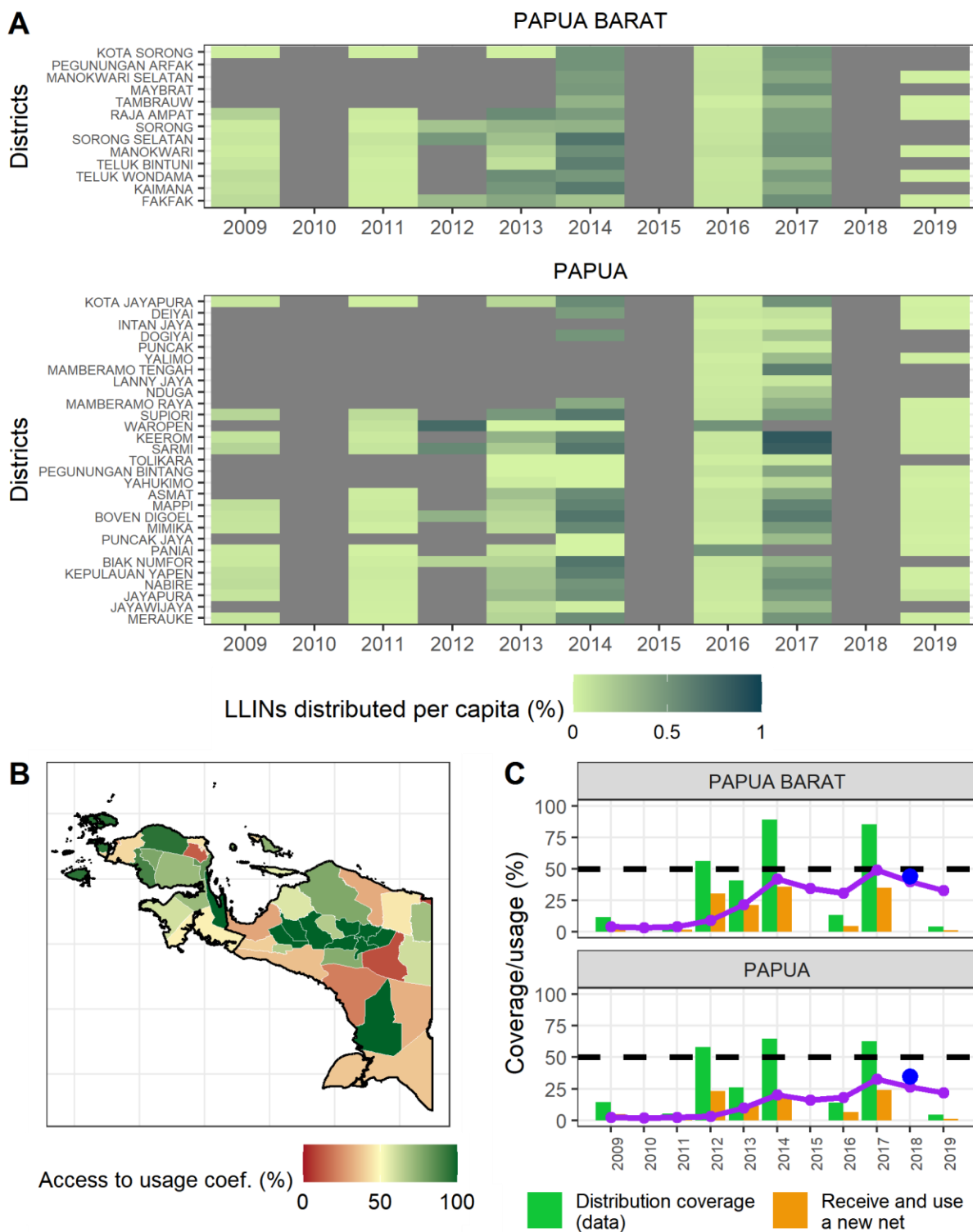


Figure 7.3. A) Annual number of LLINs distributed per capita at the district level in Papua Barat and Papua province. Grey denotes no LLIN distribution during the year; B) The district-level map of the access to usage coefficient required to match the distribution data to survey usage; and C) LLINs distribution coverage, based on distribution data (green bars) and after LLIN usage model fitting to survey data (orange bars), the modelled usage based on the fitted coverages representing end-of-year estimates of usage (purple lines), and the population LLIN usage survey data point conducted in the middle of 2018. All summarised (weighted mean) as province-level values.

7.3.3 Malaria model fitting to 2019 WHO-adjusted PfAPI per 1,000

The mathematical model of malaria was calibrated to the latest WHO-adjusted PfAPI per 1,000 (2019 data for most districts). Estimated baseline PfEIR values from the model fitting process, a proxy for inferred baseline *P. falciparum* malaria transmission receptivity in the district, are shown in **Figure 7.4**. The estimated baseline PfEIR values vary between a minimum of 0.01 in the Pegunungan Arfak district, indicating levels of baseline transmission already close to elimination, to 38 in the Sarmi district, approaching hyperendemic levels of transmission comparable to many of the highest-burden areas of transmission globally. The PfEIR estimates show a strong negative correlation with altitude (**Figure 7.4A**), which is typically characteristic of *P. falciparum* transmission patterns. However, even accounting for altitude, the baseline PfEIR are lower in Papua Barat, where some low-altitude districts have very low baseline PfEIR.

The geographical distribution of the estimated baseline PfEIR at the district level across the region (**Figures 7.4B and C**) highlights the lowland northern coastal districts of Papua province as the area with the three highest estimated baseline PfEIR values across the region (Sarmi, Mamberamo Raya, and Keerom) but are subject to a degree of heterogeneity, with data from neighbouring districts of similar elevation along the northern coast producing estimated baseline PfEIR an order of magnitude lower. Similarly, highland districts in the province were typically low but could also vary by orders of magnitude between neighbouring districts of similar altitudes. Though such micro-epidemiological variation is well documented for malaria (Baidjoe et al., 2016; Bejon et al., 2014), it should be noted that, in these examples, districts with the highest transmission are those which were amongst the most strongly affected by the case adjustment using WHO methodology (**Figure 7.2D** and **Figures S9-13** -see discussion for a summary of potential limitations to this approach).

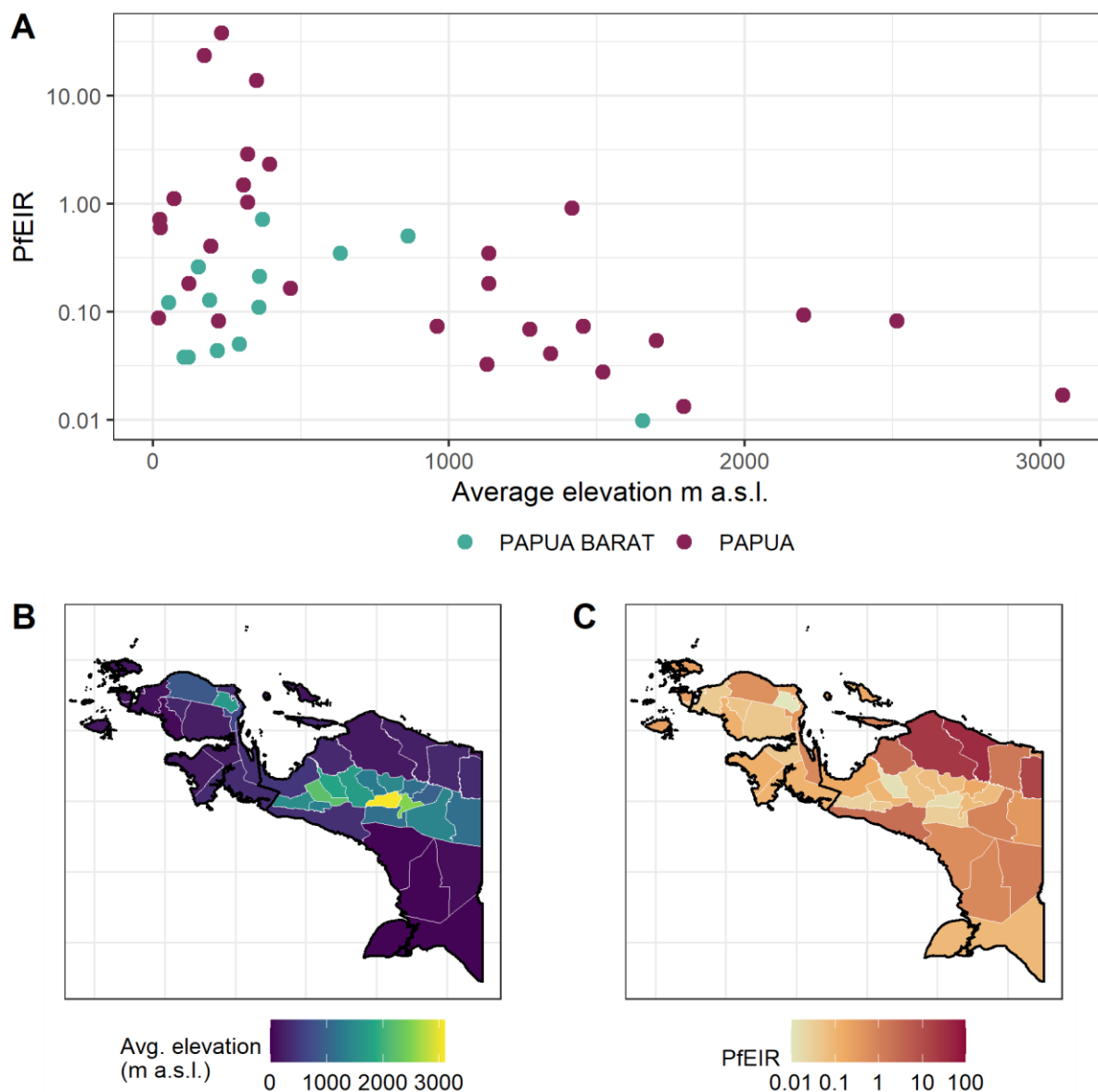


Figure 7.4. A) Scatter plot of elevation vs model estimated baseline PfEIR (on log-scale); B) District-level average elevations; and C) District-level geographical distributions of model estimated baseline PfEIR.

7.3.4 Exploring the concordance of malaria case trends between model estimates and data

The fitted mathematical models, calibrated to the most recent data after being adjusted for reporting and treatment-seeking, were used to extrapolate trends backwards. These ‘expected’ trajectories were used to assess whether the district-level inputs that parameterised the model (vector bionomics and intervention scale-up) are in any way consistent with the district-level trajectory during the ‘LLIN scale-up’ and ‘maintenance’ stages. When these district-level simulations are aggregated to the province level (**Figure 7.5A**), the magnitudes of decline in *P. falciparum* cases following the initial ‘LLIN scale-up’ stage expected by the model fall between that implied by the reported and WHO-adjusted trends. The model expects a larger relative decline in cases in Papua Barat, driven by a higher effective coverage of LLINs, but a

larger absolute decline in Papua province, driven by a higher initial baseline EIR, both of which are in qualitative agreement with WHO-adjusted trends. The model is also in qualitative agreement with the WHO-adjusted case trends throughout the subsequent maintenance stage, with a combination of attrition from a lower level of effective LLIN coverage and higher baseline endemicity, leading to a substantial resurgence in transmission in Papua province until 2017, at which point the trend is reversed following the second mass LLIN campaign. Meanwhile, in Papua Barat province, the model expects progress to be better maintained throughout, driven by higher effective coverage and helped by a lower initial baseline.

District-level maps of relative changes in PfAPI per 1,000 after the 'LLIN scale-up' stage (measuring relative changes between 2010 and 2015) and the 'maintenance' stage (measuring relative changes between 2015 and 2019) based on reported data and model estimates are shown in **Figures 7.5B** and **C**. **Figure 7.5B** compares the relative changes after the 'LLIN scale-up' stage (i.e., comparing 2010 to 2015) between the reported data and model estimates across districts (noting that a lack of district-level reporting completeness data prior to 2018 makes comparing WHO-adjusted trends at this resolution unreliable) and **Figure 7.5C** shows the equivalent maps during the maintenance stage (comparing 2015 to 2019). These patterns are less clearly aligned with the model expectations, though given reported data are unadjusted, it is difficult to assess the extent to which this could be due to the large fluctuations in reporting rates observed throughout the study period. However, the absolute magnitude of the change in cases in the data and expected by the model showed a statistically significant positive correlation (Pearson's correlation coefficient = 0.86, p-value < 0.001) and for the majority (31 out of 42) of the direction of changes in reported cases throughout the maintenance period was the same as that expected by the model (**Figure 7.5D**). Many of the remaining 11 discordant districts had historically low malaria tests or had only recently experienced a surge in malaria tests (as shown in **Figures S10** and **S11**). It is also notable that within Papua region, the model expected a tendency for larger resurgences in the higher lowland areas, due to their higher baseline transmission intensity (similar to findings from modelling of mass drug administration, MDA, (Okell et al., 2011)), a trend which is also visible within the data.

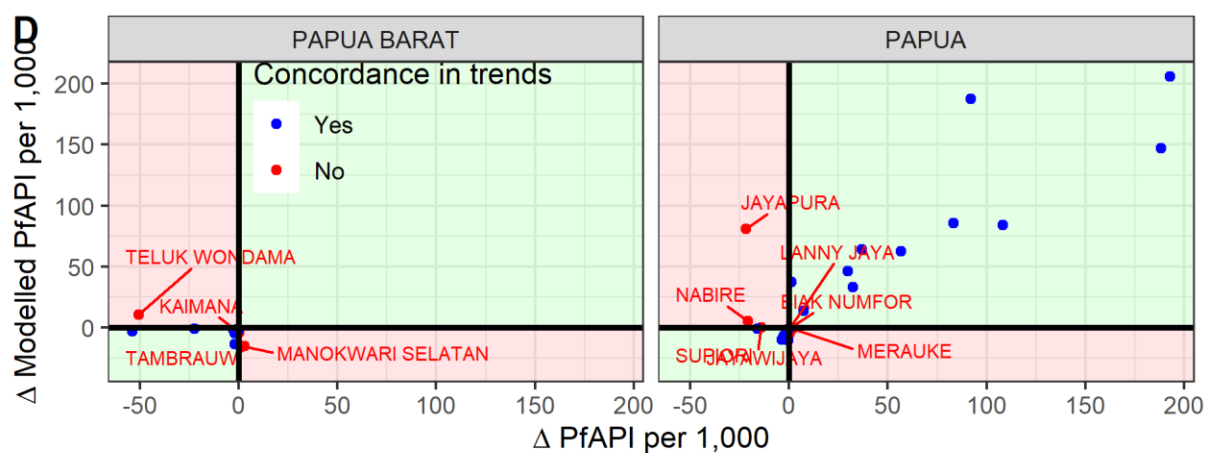
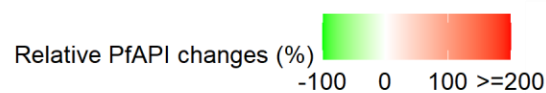
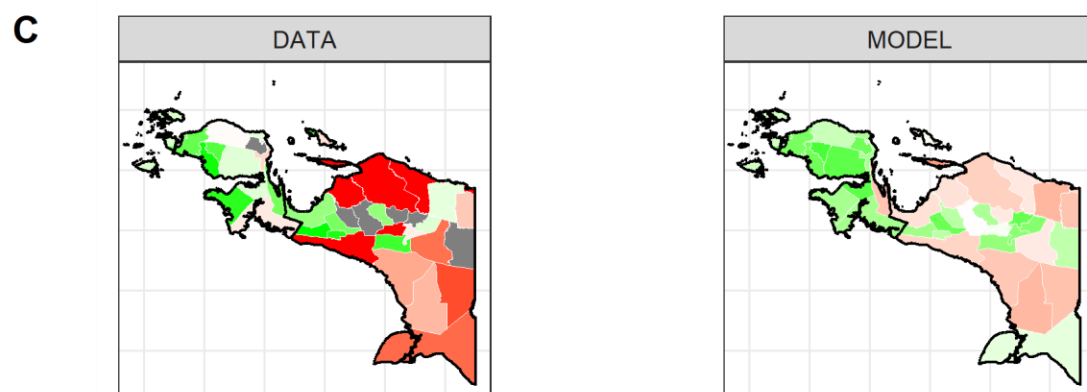
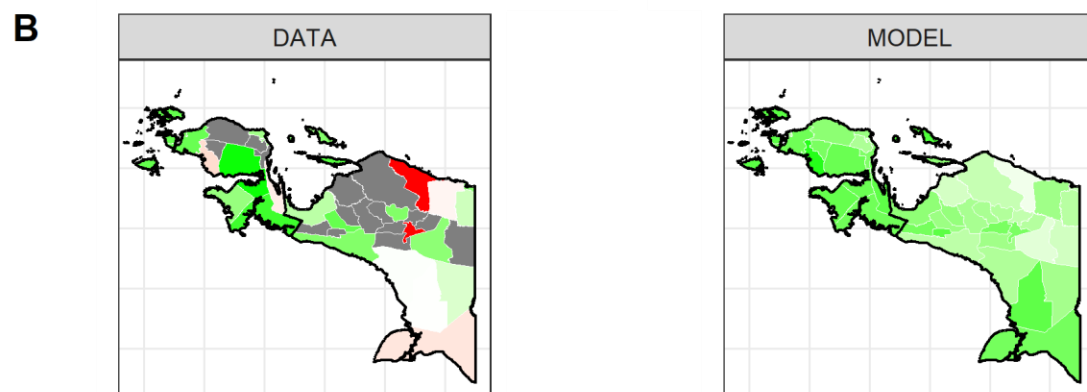
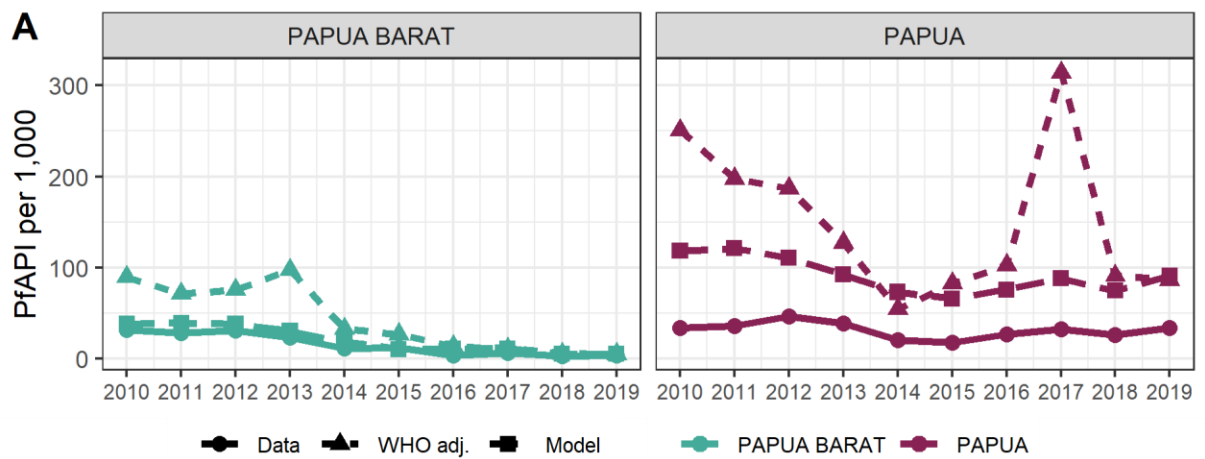


Figure 7.5. A) Province-level trajectories of PfAPI per 1,000 based on reported data, WHO-adjusted values and model estimates; B) Relative changes between reported data and modelled estimates of 2010 PfAPI per 1,000 to 2015 PfAPI per 1,000. Grey shaded areas denote no 2010 data were available as the baseline; C) Relative changes between reported data and modelled estimates of 2015 PfAPI per 1,000 to 2019 PfAPI per 1,000. Grey shaded areas denote no 2015 data were available as the baseline; and D) Concordance plots of the absolute difference of 2015 and 2019 PfAPI per 1,000 based on reported data (X-axis) and model estimates (Y-axis). Districts mentioned in red are districts with discordant data and model estimates.

7.3.5 Assessing the province-level impact of LLIN distributions

Figure 7.6A provides a summary of the cumulative absolute reductions in *P. falciparum* incidence after the first LLIN scale-up and follow-up LLIN campaigns, compared to the ‘pre-LLIN’ baseline. **Figure 7.6B** shows *P. falciparum* incidence reductions relative to the number of LLINs distributed in both provinces. These figures suggest that the reported data may have underestimated the overall reductions of *P. falciparum* incidence following the LLIN scale-up and campaigns. Additionally, the figures highlight the significantly larger magnitude of reductions in *P. falciparum* incidence in Papua compared to Papua Barat, both in terms of absolute and relative reductions. Furthermore, the figures demonstrate the increasing impact of LLIN distributions, as measured by the cumulative reductions from the ‘pre-LLIN’ stage, in terms of the absolute and relative reductions. Continued LLIN distributions during the ‘2015-2019 maintenance’ stage resulted in further estimated absolute cumulative reductions of 130 thousand and 609 thousand in *P. falciparum* incidence from the ‘pre-LLIN’ baseline, based on model estimates, for Papua Barat and Papua, respectively. In terms of the relative reductions, in Papua Barat, where malaria endemicity is lower than in Papua, the relative gains nearly doubled after factoring distributions during the ‘maintenance’ stage. However, in Papua, despite only minimal changes in the relative gains after factoring distributions during the ‘maintenance’ stage, the value of continued LLIN distributions remained considerably higher than in Papua Barat.

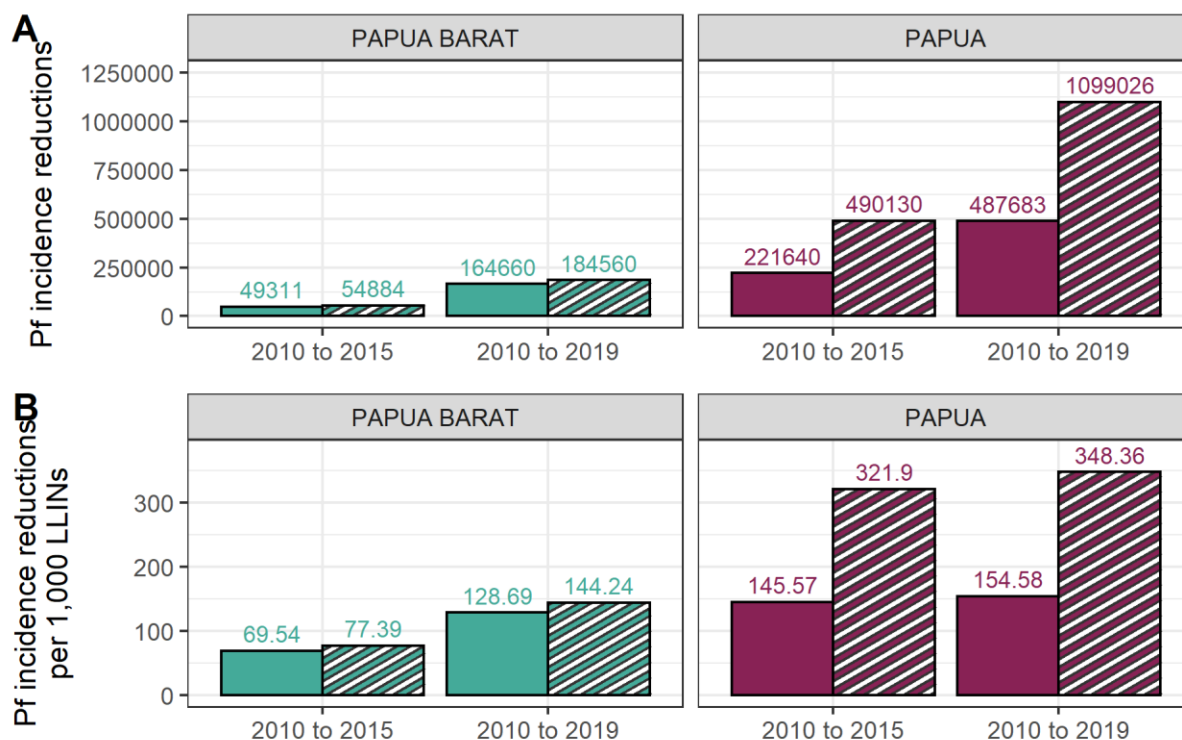


Figure 7.6. A) *P. falciparum* incidence reductions after the ‘LLIN scale-up’ stage and the following LLIN campaigns in 2017; B) *P. falciparum* incidence reductions per 1,000 LLINs distributed after the ‘LLIN scale-up’ stage and the following LLIN campaigns in 2017. Shaded bars denote values from model estimates, while solid bars denote values from reported data.

7.4 Discussions

At first glance, despite continued efforts to eliminate malaria through the scale-up of multiple interventions, it may appear that the Papua region of Indonesia experienced stagnation or even a resurgence in reported malaria cases in the second half of 2010-2019. Although these overall trends suggest that progress in reducing malaria has stagnated, a closer look reveals a more nuanced picture. There are highly divergent trends in the reported cases between the two provinces within the region, with Papua Barat province reporting sustained reductions throughout the decade. In contrast, reported malaria cases in Papua have remained largely static. A closer examination at the district level suggests that the explanation for these divergent trends is multi-faceted.

Firstly, my analysis of surveillance data suggests that improvements in surveillance systems in Papua province over the decade, where reporting and treatment-seeking rates were particularly low in 2010, have likely masked the extent of declines in malaria incidence in the region. Secondly, the examination of LLIN distribution and usage data suggests that Papua Barat province has achieved a higher effective coverage of LLINs than Papua province over the same period. Thirdly, the modelling analysis suggests that in Papua province, despite not seeing sustained declines in malaria incidence as were seen in Papua Barat province, the

gains in terms of absolute and relative reductions in *P. falciparum* incidence were much higher in magnitude.

These findings highlight the importance of carefully interpreting trends in routine surveillance data, particularly within the context of increased surveillance efforts, which may lead to potentially misleading conclusions about the impact of interventions. Furthermore, they highlight that the success of interventions should not be solely defined by the resulting surveillance metric trends, i.e., incidence, following their implementations. Considering the context of transmission intensity in which these interventions are implemented is important. For example, LLIN distributions in Papua province may not have resulted in sustained declines in malaria incidence. However, their impact in reducing malaria incidence relative to the number of LLINs distributed remains very high. Finally, the study reveals that the effective LLIN coverage tends to be lower in settings with a higher malaria transmission potential at the baseline in the Papua region. This suggests that in such settings, future distributions of LLINs could benefit from better allocations and prioritisation of resources to optimise the outcomes of interventions.

I found a negative correlation between the estimates of baseline PfEIR of all districts in the Papua region and their average altitudes, supporting the model's ability to capture the underlying malaria transmission trends while accounting for intervention impacts and local mosquitoes' bionomics. However, unexplained differences in baseline transmission between the two provinces still require further investigation. Factors other than altitude, such as land use changes and socioeconomic indicators, may be critical in explaining these differences (Fornace et al., 2021; Hanandita & Tampubolon, 2016). For example, throughout 2001-2018, Papua province experienced higher rates of forest loss and plantation expansion than Papua Barat province, with a dramatic increase in the early 2010s and peaked in 2015 (Gaveau, 2018). While the impact of these changes on malaria transmission is complex and context-specific (Fornace et al., 2021), they could have affected local mosquito vectors' dynamics and their exposure to human populations. Additionally, differences in socioeconomic factors, represented by proxy of some indicators, such as human development index, housing and sanitation qualities, formal sector workers proportion, urban area proportion, and people's educations, may contribute to the differences in risks of contracting malaria between the two provinces (Hanandita & Tampubolon, 2016; Vice-presidential Secretariat of The Republic of Indonesia & National Team for the Acceleration of Poverty Reduction, 2021).

There is a limitation related to the contribution of surveillance types that could influence the case counts of the routine malaria surveillance data. The available data does not differentiate between malaria cases detected through active case detection (ACD) and passive case detection (PCD), a distinction that could have potential implications for our understanding of

malaria transmission dynamics. This distinction is made only in individual-level data, which was not accessible for this study. The relative reliance on ACD or PCD may vary by district, potentially influencing local case counts.

Finally, there are several potential avenues for future works building on from this study. First, a more nuanced adjustments of malaria cases could be developed based on the WHO case-adjustment algorithm to account for the differences in testing levels and trends over time at the district level. This would allow for better case adjustments for districts with historically low testing rates or those recently experiencing surge in malaria testing. Second, future studies could further refine our understanding of malaria trends in Papua by including the relative contribution of ACD and PCD on the reported cases in each district. Third, the calibrated model can be used to explore future potential malaria elimination strategies in the region, such as the introduction of more frequent mass LLIN campaigns in high-transmission lowlands. Fourth, future analysis will also benefit from the enhancement of the understanding of how malaria trends in the Papua region of Indonesia matches with the PNG side. Leveraging the power of combining information from the two regions will hopefully increase our understanding of how-to better control and finally eliminate malaria from this region. Fifth, since the LLIN-related aspects of the modelling framework used in this study were based on parameters and models fitted to data and experiments (e.g., experimental hut trials) from African countries, performing similar experiments and generating similar data in the Papua region would be important for future implementation of this modelling framework. Lastly, further analysis is needed, incorporating models of *P. vivax* transmission, as this analysis only focused on *P. falciparum* which accounts for approximately half of the malaria burden in the region.

7.5 Conclusions

This chapter highlights the importance of a high-resolution analysis of malaria transmission in the Papua region of Indonesia, which provides important insight into the malaria situation in the region during the LLIN scale-ups and maintenance stages. The findings suggest that progress towards malaria elimination varied at the province and district levels, and the resurgence of malaria transmission in the region was largely driven by districts with high transmission potential and lower LLIN utilisation in Papua province. This study also demonstrates how surveillance and mathematical model can complement each other to enhance our understanding of the transmission and burden of malaria. Future research should aim to develop more nuanced adjustments of reported malaria data, explore potential malaria elimination strategies in the region, enhance the regional understanding of malaria transmission by comparing the trends with the PNG side, parameterise the model with local data, and incorporate *P. vivax* transmission model.

Chapter 8: Discussions and conclusions

8.1 Thesis aims and objectives

This thesis aims to utilise statistical and mathematical modelling techniques to analyse surveillance data of infectious diseases in Indonesia, gaining insights to inform infectious disease control programs in the country. In the context of COVID-19 data analysis, the aim is to utilise modelling techniques to see whether an alternative dataset based on syndrome-based mortality (funerals with COVID-19 protocol, C19P) can provide a more comprehensive understanding regarding transmission and burden during an ongoing epidemic, particularly in situations where there was limited testing and suboptimal reporting from the traditional epidemiological surveillance data. For the malaria data analysis, the aim is to utilise modelling techniques to gain insights from 10-year malaria surveillance data in Indonesia, which includes measuring progress from intervention scale-ups, finding the plausible driver of the progress, and developing a framework to utilise a mathematical model of malaria and high-resolution routine malaria surveillance data to estimate malaria burden and intervention impacts in the high-endemic malaria region. Though these two halves of the thesis concern, at face value, very different situations – one being an emerging global pandemic with limited but rapidly changing intervention strategies and the other one being a centuries-old disease with established drugs, vaccines, and interventions – I discovered several parallels during my analysis that I believe to be relevant across various infectious disease contexts, especially those dealing with routine surveillance data.

8.2 Summary of findings

In **Chapters 2, 3, and 4**, I applied various statistical and mathematical models to analyse data from the COVID-19 epidemic in Jakarta and Java Island. In **Chapter 2**, I used a branching process statistical model to estimate the effective reproduction number (R_t) of SARS-CoV-2 in Jakarta. I applied the model to reported COVID-19 cases, reported COVID-19 deaths, and C19P funerals, accounting for the delays between the onset of symptoms and tests and the onset of symptoms and deaths. The results showed that estimates of R_t based on C19P funerals data reflect an earlier decline in COVID-19 transmission in the population, which is in line with the decline in population mobility. These estimates also showed a more sustained decline in transmissibility in response to non-pharmaceutical interventions (NPIs) compared to estimates from reported COVID-19 cases and deaths. Additionally, the analysis supports the suggestions that COVID-19 might have circulated before the first cases were announced in early March 2020. This chapter highlights the benefits of using syndromic measures of

mortality, such as C19P funerals data, to understand the past burden and current dynamics of the COVID-19 epidemic.

In **Chapter 3**, I developed a metapopulation model of COVID-19 spread to analyse the spread of COVID-19 in the districts of Java Island and evaluate the impact of NPIs implemented during the first wave of the COVID-19 epidemic. The analysis shows that the NPIs, particularly during Ramadan, helped slow down the spread of COVID-19 to rural districts. In addition, the NPIs also prevented a larger potential burden in these rural districts, where populations are older and healthcare capacities are poorer.

In **Chapter 4**, I compared COVID-19 mathematical model outputs calibrated to confirmed COVID-19 deaths data and suspected COVID-19 deaths data at the province level in Java Island. The analysis revealed that the attack rate estimates based on the model calibrated to suspected deaths data were 2-3 times higher than those based on confirmed COVID-19 deaths data. These differences in the estimates of total burden could affect future scenario simulations from models. In addition, the future scenario projections also indicated that reducing transmission in the population during the early period of vaccinations would lead to a higher proportion of people receiving protection before they get infected, which would have an incremental impact on the vaccination campaign.

The malaria analysis started in **Chapter 5**. In this chapter, I analysed ten years of district-level malaria routine surveillance data using statistical models to show the changes in the malaria landscape in Indonesia. At the national level, reported malaria cases were halved after ten years, while continuous declines were observed in almost all regions except Papua, where progress has stagnated since 2015. Additionally, the analysis showed changes in the demographic of malaria cases, with increases in older populations and a shift towards a male-dominant case pattern.

In **Chapter 6**, I utilised a plausibility design framework incorporating the Bradford Hill causality criteria to assess the plausibility of LLIN mass distribution campaigns throughout 2010-2019 as the main driver of the decline in malaria incidence across the country. The framework involved a literature review and analyses of model simulations and routine surveillance data and found strong evidence supporting the plausibility that LLIN mass distribution campaigns were the main driver of the observed declines in malaria transmission in Indonesia. Additionally, the analysis also identified that scale-ups of other interventions, such as routine LLIN distribution in children and pregnant women, ACT treatment, indoor residual spraying, larval control, environmental management, laboratory confirmation, and screening in pregnant women throughout the period, may have an important role in maintaining the decline and preventing resurgences in malaria cases.

In **Chapter 7**, I focused on Papua, the region with the highest malaria endemicity in the country, where progress towards malaria elimination has stagnated, and resurgences of malaria cases have been observed following scale-ups of LLIN distributions. I developed a framework to calibrate and simulate the Imperial College malaria model to *P. falciparum* incidence data from routine surveillance at the district level, which was adjusted using the WHO case-adjustment algorithm accounting for underreporting of clinical incidence due to the treatment-seeking behaviour of the population and incomplete reporting. The analysis shows that progress towards malaria elimination in this region varies at both province and district levels, highlighting the value of more high-resolution analysis of the region. Stagnation and resurgence of malaria cases in the region were largely driven by the malaria case trajectories of high-endemic districts in Papua province, which is also likely exacerbated by lower utilisations of the distributed LLINs in those districts. Furthermore, this chapter also demonstrates the importance of combining analysis of routine surveillance data with mathematical modelling to better understand the transmission and burden of malaria.

Overall, I demonstrated how modelling techniques, combined with infectious disease surveillance data, can enhance our understanding of infectious disease transmission and burden, whether in an emerging epidemic setting like COVID-19 or an endemic disease such as malaria. The models applied to evaluate the impact of interventions against these diseases share similarities in their fundamental structure and approach – both are grounded in understanding the non-linear processes underlying disease transmission dynamics and intervention impacts. By understanding those processes, the models can be effectively linked with surveillance data, allowing for calibration and estimation of key parameters explaining the transmission potential of those diseases, such as the basic reproduction number (R_0) for COVID-19 and the baseline Entomological Inoculation Rate (EIR) for malaria, under conditions of no interventions and immunity within the populations.

Moreover, this study also highlights the parallels that can be drawn from the analysis of these two diseases that are relevant in the broader context of infectious diseases. First, there is a need to look beyond raw numbers from surveillance data and consider factors, such as surveillance trends and alternative metrics guided by the underlying epidemiology of the disease, when interpreting observed trends. For instance, utilising symptom-based surveillance data or analysing age patterns within cases can aid in identifying meaningful trends. Second, it is important to understand the underlying highly non-linear processes that link disease transmission to burden and risk and how it affects intervention impact. This study provides examples, such as the varying potential impact of future vaccination strategies under different NPI intensities and how baseline malaria endemicity influences the impact of an LLIN campaign. Finally, this work highlights the importance of understanding counterfactuals when

evaluating the impact of past interventions or assessing the potential impact of future intervention strategies.

In summary, these modelling approaches can be extremely beneficial in various public health situations – for instance when proposing new interventions or anticipating changes in policy or funding that may affect the availability or deployment of existing interventions. By simulating different scenarios, models can assist policymakers in understanding the potential impact of their decisions, thereby facilitating more informed decision-making. Furthermore, these models can also be used for retrospective analysis to determine the impact of interventions in situations where direct measurement is not possible due to the absence of a counterfactual.

In low- and middle-income countries (LMICs), there were challenges in reporting COVID-19 mortalities due to many factors, such as weak data recording and vital registration systems, variations in testing policies and implementation of WHO guidelines, limited testing capacities, and political interferences (Feyissa et al., 2021; Whittaker et al., 2021). The results from the COVID-19 work also served as additional evidence, as highlighted by other studies in other LMICs (Alves et al., 2020; Besson et al., 2021; I. R. Elyazar et al., 2020; Endris et al., 2021; Ghafari et al., 2021; Levin et al., 2022; Mwananyanda et al., 2021; Watson et al., 2021), on how underreporting of deaths limited our understanding of the true extent of COVID-19 burdens and impact and how to use alternative datasets to overcome this challenge (Whittaker et al., 2021). As was also assessed in this thesis, underreporting of deaths prevents us from assessing the pandemic's maturity, which affects our ability to assess the relative contributions of social restrictions and population immunity in declining transmission (Whittaker et al., 2021). This has implications for how governments formulate their future policies, e.g., whether to maintain social restrictions weighing the societal costs and health benefits of such restrictions and how to equitably distribute vaccines in the population (Hogan et al., 2021; Whittaker et al., 2021). Additionally, O'Driscoll et al. provided a large-scale analysis of the national-level COVID-19 infection fatality ratio (IFR) across many countries, including Indonesia, based on seroprevalence data, further reinforcing the discussion on COVID-19 mortality underreporting in LMICs (O'Driscoll et al., 2021). Furthermore, this body of evidence highlights changes and improvements needed to assess the true burden of the COVID-19 pandemic across the globe and prepare for the next pandemic. In the short term, assessment of excess mortality, publication of burial data, scale-up of collection and harmonisation of all COVID-19-related data and set up of community surveys where feasible could be done to improve the understanding of countries' COVID-19 burden. However, in the long term, investments in improving civil registration and vital statistics systems' capacity and coverage, adopting technological innovations to implement testing regimes of novel pathogens quickly, and developing robust safeguards to avoid distortion of official statistics for political motives are

needed to ensure the essential data are available to better response for future pandemics (Whittaker et al., 2021).

In the context of malaria in Indonesia, this thesis provides a more comprehensive assessment of the progress towards malaria elimination in Indonesia using modelling techniques and routine surveillance data compared to the published information by the NMCP (Fajariyani & Anggraeni, 2020; Sitohang et al., 2018). The analyses in this thesis show how scale-ups of interventions, particularly LLIN mass distribution campaigns, since the commitment to eliminating malaria started in 2009, have significantly reduced malaria cases across the country. However, extra caution is needed to address problems in the Papua region where progress towards elimination stagnated. Additionally, the framework to calibrate and apply malaria models introduced in this thesis could be a useful solution to add additional evidence and analysis for policy formulations regarding malaria elimination programs, allowing the use of routine surveillance data rather than prevalence surveys and addressing issues related to calibration to incidence data as were highlighted in previous studies (Champagne et al., 2022; Nekkab et al., 2021; Silal et al., 2014; Ukawuba & Shaman, 2022). Successful calibration and validation of the model would allow further assessment of potential introductions of novel malaria interventions and optimal resource allocations to maximise gains in burden reductions.

8.3 Limitations and future directions

There are limitations related to the results presented in this thesis. First, for the COVID-19 analyses, no suitable data could be used to validate the analyses when the study was conducted. Some prevalence survey results were available afterwards (Ariawan et al., 2022; Herlinda et al., 2021; Megasari et al., 2021); hence I made rough comparisons between the results and those newly available data in the discussion section. There was also no suspected death data at the district level, making validation of mortality projections at this level impossible.

Furthermore, in **Chapter 2**, adjustments of reported COVID-19 cases and deaths to their respective onset of symptoms dates may not account for the delays between the event dates (either confirmation test dates or dates of deaths) and the reporting dates due to the difficulty to assess whether the date of reporting matches the date of each event. This delay factor likely affected the accuracy of R_t estimates based on these data, a factor that was not present in the burial data that accurately presented the burial dates, occurring within 24 hours after death. However, this further highlights the utility of such alternative data during an emerging epidemic. Additionally, there was a limitation regarding the data reconstruction method used, which caused some loss of information in the tail end of the reconstructed data due to the number of events that had not yet happened or been reported. In the analysis, this was remedied by

removing the tail end of the reconstructed data, a 7-day period, containing high uncertainty of estimated symptom onset frequencies.

In **Chapter 3**, I estimated the potential burden of several scenarios of COVID-19 transmission and highlighted the extent to which these could overwhelm available healthcare capacity. However, I was not able to quantify the potential additional mortality this health-system impact would represent as quantitative parameters determining the severity of COVID-19 in those who do not access care was, and remain, poorly characterised. Furthermore, the spline model used in this chapter did not account for the decoupling between population mobility and virus transmissibility after the first PSBB was over, limiting our ability to directly quantify the trajectory of the pandemic following this period.

Finally, in **Chapter 4**, there are limitations related to the future scenario projections due to the uncertainty in the level of population immunity required to achieve herd immunity. These uncertainties could come from the strength and duration of the individual immune response, heterogeneity in population mixing patterns, and changes in the inherent characteristics of the virus due to the introduction of variant of concerns in 2021.

Those limitations related to data availability demand government institutions (or other responsible institutions) to change their data-sharing and dissemination practices, especially during an emergency where the availability of such data becomes crucial. Having good data-sharing and dissemination practices, as shown by the collaborators in the Jakarta Health Office through their COVID-19 data monitoring website, requires political commitments, which is out of the scope of this thesis. However, this thesis and the published paper related to the COVID-19 analyses could be one of the pieces of evidence for advocacy related to data sharing during the period of emergency. Nevertheless, due to the good disease surveillance practice and relative easiness of collaborations of the Jakarta Health Office, many potential research and collaborations can be pursued. Their disease surveillance websites contained spatiotemporal data of disease incidence from hospital-based surveillance and primary health centre-based surveillance with infectious diseases surveyed, ranging from rabies to dengue fever (Bidang Pencegahan dan Pengendalian Penyakit Dinas Kesehatan DKI Jakarta, 2022). This richness of data can potentially be utilised for further research related to routine surveillance and modelling, ranging from outbreak detection to cluster analysis.

The limitations in the malaria analysis chapters of this thesis are largely inherent to the biases that come from routine surveillance data and the sources of data collected within them. To address the biases, I used modelling techniques, case data adjustments, and sensible analysis frameworks when analysing the data while providing some nuances related to what extent the results were valid. However, there was not much that could be done related to the type of surveillance that became the sources of the malaria incidence data, for example, whether the

proportions of those data came from passive case detections, active case detections, or mass blood surveys, among others. How the data were collected in the first should affect how the data may be interpreted, but such classifications are not available yet to the data analysed.

The plausibility assessment for the impact of LLIN mass distribution campaigns on reducing malaria incidence was done at the region level, which may not capture the variability occurring at the lower geographical levels. Moreover, the routine malaria surveillance data may be subject to biases and limitations regarding reporting quality, completeness, and consistency. To overcome those biases, the changepoint analysis was conducted on two metrics, incidence rate and test positivity ratio, as indicators of malaria burden and transmission. However, those two metrics may not fully capture the complexity of the malaria dynamics in the country and its regions. Finally, the study relied on a literature review of studies coming from other countries and observational evidence from routine surveillance data. Further studies involving experimental study designs may be needed to assess the effectiveness of LLINs that account for the local characteristics of malaria transmission in Indonesia.

Finally, there are several limitations in the analysis of malaria transmission and burden in the Papua region in **Chapter 7**. First, the WHO case-adjustment method did not account for the differences in testing levels and trends over time. This would affect the adjusted case counts for districts with historically low testing rates or those recently experiencing surges in malaria testing. Second, the mathematical model used for the analysis was parameterised using data and parameters largely from the African continent, which may not fully capture the unique dynamics of malaria transmission in Papua. Third, the study focused primarily on *P. falciparum* transmission and did not incorporate mathematical models for *P. vivax* transmission, another important malaria parasite species in the region.

Those limitations due to the data availability and limitations might be remedied by the fact that the NMCP has been collecting individual data on malaria incidence in the past few years, allowing them to capture the sources of surveillance type for each incidence, as well as more details related to their demographics (Subdirektorat Malaria Kementerian Kesehatan Republik Indonesia, 2018). For example, these data would allow the analysis of age-incidence more granularly and the analysis of the age-malaria species relationship. Additional reliable data would also allow quantitative validation of the model performance. These would open future detailed analyses of the routine surveillance data and ensure validated modelling output. Furthermore, adapting the developed models of *P. vivax* to routine surveillance data in Indonesia and exploring these models to inform policies specific to *P. vivax* control would be interesting future work (White et al., 2018). Finally, I am interested in diving into the biology of *Plasmodium* co-infections and how to appropriately model them (Holzschuh et al., 2022). With

both *P. falciparum* and *P. vivax* being dominant species in Indonesia and neighbouring Papua New Guinea, these explorations might yield important policy implications in the future.

8.4 Conclusions

In conclusion, the results of this thesis demonstrate the importance of utilising both modelling and data to inform policy in the control of infectious diseases. The use of models and data can provide important insights into the current transmission of the disease, evaluate past control measures, and simulate future scenario projections to assess the potential impact of interventions. Furthermore, models can aid in the interpretation of surveillance data, which is often subject to biases due to limitations in testing capacity, incomplete and delayed reporting, and heterogeneity in population behaviour (i.e., treatment-seeking behaviour). Additionally, alternative data sources, such as syndromic measures of mortality, can provide a more comprehensive picture of an epidemic, especially in the early phase of an epidemic when testing capacity is limited and data reporting is imperfect. The COVID-19 pandemic has highlighted the vital role that modelling and data analysis can play in informing policy decisions related to infectious disease control. The increasing popularity of modelling during this time may lead to a shift towards an evidence-based approach in policymaking that further emphasises the importance of utilising both modelling and data to inform policy in infectious disease control, especially in Indonesia.

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Appendix

Chapter 1 supplementary materials

Components of Imperial *P. falciparum* mathematical model

Human component of the malaria transmission model

The model divided the human population into six states. They are susceptible (S), treated clinical disease (T), untreated clinical disease (D), asymptomatic patent infection (A), sub-patent infection (U), and protected by a prophylactic effect from prior treatment (P). Each individual moves between states based on the assigned rates and probabilities. The schematic of the human component of the model is shown in **Figure S1.1**. Susceptible individuals (S) become infected at a rate of λ , which is a product of the ratio of vector to human, the mosquito biting rate that varies with age, the proportion of infected mosquitoes, and the probability of infection from mosquito bites that accounts for age profile and previous exposures (immunity in the human population will be explained in detail in the next section). Following infections, individuals will go through the latent period of the liver stage infections and then proceed to either develop clinical diseases (with a probability of φ depending on the level of immunity to disease) or develop patent (blood parasitaemia can still be detectable under microscopy) asymptomatic infection (with a probability of $1 - \varphi$). Those who develop clinical diseases can get treated successfully (with a probability of p_{treat}) and then moved to state T , clearing their infections. Depending on drug types, they will move to the period of prophylactic protection, P (with a rate of r_T), and then return (with a rate of r_P) to state S , susceptible to new infection. Those who do not get treated (with a probability of $1 - p_{treat}$) proceed to the clinical disease state, D , and then clear the symptoms to become patently asymptomatic, A , with rate r_D . From the patently asymptomatic state, individuals will move to the sub-patent asymptomatic state, U , with rate r_A that depends on the level of anti-parasite immunity. The sub-patent asymptomatic individuals will clear their infections and return to being susceptible with rate r_U . The model allows for superinfection, which is acquiring a new infection while still being infected, for individuals in the A and U states.

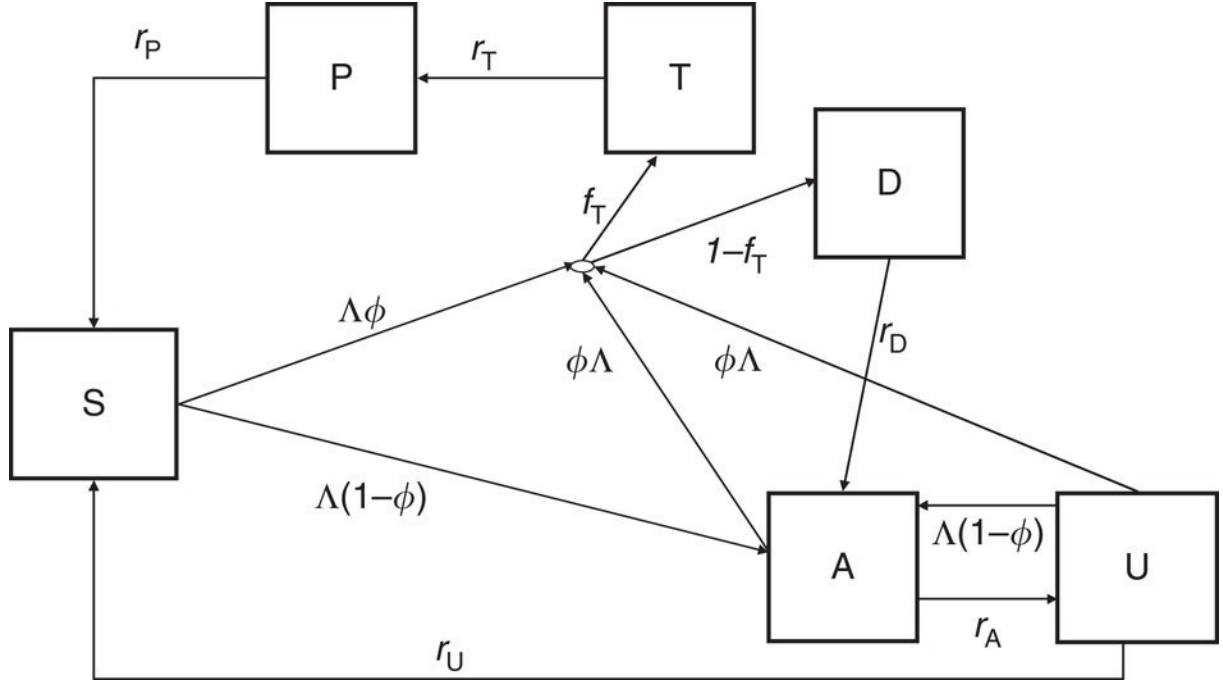


Figure S1.1. The flow diagram of the human component of the Imperial *P. falciparum* malaria model. The figure was reproduced from Griffin et al. (Griffin et al., 2014).

The differential equations of the human component of the model, with t representing time and a representing age, are as follows:

$$\frac{\partial S}{\partial t} + \frac{\partial S}{\partial a} = -\lambda(t - d_E)S(t) + r_P P(t) + r_U U(t)$$

$$\frac{\partial T}{\partial t} + \frac{\partial T}{\partial a} = \phi p_{treat} \lambda(t - d_E)(S(t) + A(t) + U(t)) - r_T T(t)$$

$$\frac{\partial D}{\partial t} + \frac{\partial D}{\partial a} = \phi(1 - p_{treat}) \lambda(t - d_E)(S(t) + A(t) + U(t)) - r_D D(t)$$

$$\frac{\partial A}{\partial t} + \frac{\partial A}{\partial a} = (1 - \phi) \lambda(t - d_E)(S(t) + U(t)) + r_D D(t) - \phi \lambda(t - d_E) A(t) - r_A A(t)$$

$$\frac{\partial U}{\partial t} + \frac{\partial U}{\partial a} = r_A A(t) - r_U U(t) - \lambda(t - d_E) U(t)$$

$$\frac{\partial P}{\partial t} + \frac{\partial P}{\partial a} = r_T T(t) - r_P P(t)$$

Each compartment is further stratified by age (indexed by i) and heterogeneity compartments (indexed by j), but those indexes were suppressed for clarity. The biting rate is assumed to vary with age, reflecting the relationship between the probability of biting with age-related lifestyle and skin-surface area. Therefore, the biting rate at age i is defined as:

$$\psi_i(a) = 1 - \rho \exp\left(-\frac{a_i}{a_0}\right)$$

where ρ and a_0 are parameters that determine the relationship between age and biting rate, each individual is assumed to have a relative biting rate of ζ_j , relative to their age, which is drawn from a log-normal distribution with a mean of 1:

$$\log(\zeta_j) \sim N\left(\frac{\sigma^2}{2}, \sigma^2\right)$$

The entomological inoculation rate (EIR), which measures the rate at which people are bitten by infectious mosquitoes, $\varepsilon_{i,j}$, is defined as:

$$\varepsilon_{i,j} = \varepsilon_0(t) \zeta_i \psi_i(a)$$

where $\varepsilon_0(t)$ is the EIR measured for adults at time t . Hence, the force of infection, $\lambda_{i,j}$, accounting for the probability that an infectious bite leads to a patent infection, b_i , is defined as:

$$\lambda_{i,j} = b_i \varepsilon_{i,j}$$

Incorporation of human immunity in the model

The acquisition and loss of immunity in humans are dynamically modelled as a function of exposure and age. There are three immunity types modelled:

- 1) pre-erythrocytic immunity (I_B), which reduces the probability of the establishment of an infection following an infectious bite;
- 2) acquired clinical immunity (I_{CA}) and maternal clinical immunity (I_{CM}), which reduce the probability of developing clinical disease upon infection; and
- 3) detection immunity (I_D), which reduces the parasite load and thus reduces the probability of detection by diagnostic tests and the probability of onwards transmission to mosquitoes).

The three types of acquired immunities I_B , I_C , and I_D , are assumed to start from zero at birth. The detailed explanation of the dynamics of these three types of immunities within the model are as follows:

Pre-erythrocytic immunity – In a population exposed to an EIR of $\varepsilon_{i,j}(t)$, the pre-erythrocytic immunity (I_B) is dynamically modelled as a function of age and time with the following partial differential equation:

$$\frac{\partial I_B}{\partial t} + \frac{\partial I_B}{\partial a} = \frac{\varepsilon}{\varepsilon u_B + 1} - I_B/d_B$$

where u_B is a parameter that limits at which immunity to infection cannot be boosted following the previous boost from infection, and d_B is the duration of immunity to infection. The probability of infection, given the level of pre-erythrocytic immunity, I_B , is modelled as a Hill function:

$$b = b_0 \left(b_1 + \frac{1 - b_1}{1 + \left(\frac{I_B}{I_{B0}} \right)^{\kappa_B}} \right)$$

where b_0 is the probability of infection without immunity, $b_0 b_1$ is the minimum probability, and I_{B0} and κ_B are the scale and shape parameters for the Hill function.

Clinical immunity – The acquired clinical immunity (I_{CA}) in a population exposed to an EIR of $\varepsilon_{i,j}(t)$ is dynamically modelled as a function of age and time with the following partial differential equation:

$$\frac{\partial I_{CA}}{\partial t} + \frac{\partial I_{CA}}{\partial a} = \frac{\lambda}{\lambda u_c + 1} - I_{CA}/d_c$$

where u_c is a parameter that limits at which clinical immunity cannot be boosted following the previous boost from infection, and d_c is the duration of clinical immunity. The maternally acquired immunity (I_{CM}) is assumed at birth to be the proportion (P_{CM}) of the level of immunity present in a 20-year-old woman ($I_C(20, t)$) living in the same location and decaying at a constant rate ($1/d_M$):

$$\frac{\partial I_{CM}}{\partial t} + \frac{\partial I_{CM}}{\partial a} = -\frac{I_{CM}}{d_M}, I_{CM}(t, 0) = P_{CM} I_{CM}(20, t).$$

The total clinical immunity (I_C) by age and time is defined as the total acquired and maternal clinical immunity: $I_C = I_{CA} + I_{CM}$. The probability of acquiring clinical disease upon infection, given the level of clinical immunity, I_C , is modelled as a Hill function:

$$\phi = \phi_0 \left(\phi_1 + \frac{1 - \phi_1}{1 + \left(\frac{I_{CA} + I_{CM}}{I_{C0}} \right)^{\kappa_C}} \right)$$

where ϕ_0 is the probability of acquiring clinical disease without immunity, $\phi_0 \phi_1$ is the minimum probability, and I_{C0} and κ_C are the scale and shape parameters for the Hill function.

Detection immunity – The detection immunity (I_D) in a population exposed to an EIR of $\varepsilon_{i,j}(t)$ is dynamically modelled as a function of age and time with the following partial differential equation:

$$\frac{\partial I_D}{\partial t} + \frac{\partial I_D}{\partial a} = \frac{\lambda}{\lambda u_D + 1} - I_D/d_D$$

where u_D is a parameter that limits at which detection immunity cannot be boosted following the previous boost from infection, and d_D is the duration of detection immunity. The probability of detection of asymptomatic infection (A), given the level of detection immunity, I_D , is modelled as follows:

$$q = d_1 + \frac{(1 - d_1)}{\left(1 + \left(\frac{I_D}{I_{D0}}\right)^{\kappa_D} f_D\right)}$$

where d_1 is the minimum probability of detection, and I_{D0} and κ_D are the scale and shape parameters for the Hill function. f_D represents an age-dependent function for the detectability given by:

$$f_D = 1 - \frac{(1 - f_{D0})}{\left(1 + \left(\frac{a}{a_D}\right)^{\gamma_D}\right)}$$

Mosquito component of the malaria transmission model

The mosquito component of the model is based on the compartmental model of *Anopheles gambiae* life cycle and population dynamics (White et al., 2011). The framework explicitly models the life cycle from the aquatic to adult mosquito parts. The aquatic part (L) starts with the early larval instar stage (E_L), which includes the eggs and the first two larval instar stages. They then develop and move to the late instar stage (L_L), which includes the third and fourth larval instar stages. The larvae then develop into the pupal stage (P_L), becoming female adult mosquitoes (M). The average duration in the E_L , L_L and P_L compartments are d_{E_L} , d_{L_L} and d_{P_L} , respectively. The model assumed that half of the emerging adult mosquitoes are female. Furthermore, the model stratified the mosquito model into the dominant mosquito species in the region modelled, indexed with v , but suppressed for simplicity in the following explanations and equations.

The adult female mosquitoes are stratified according to their *P. falciparum* infection status, whether they are susceptible (S_M), exposed (E_M), or infectious (I_M), following an extrinsic incubation period (EIP). Mosquitoes may be infected if they blood feed into humans in the treated clinical disease (T), untreated clinical disease (D), patent asymptomatic (A), or sub-patent asymptomatic (U) states. Upon infection, they will go through their latent period (E_M) with a fixed length of τ_M and then become infectious to human (I_M) until they die. The full life cycle of the aquatic stages and adult stages of mosquitoes, including their infection status, is represented by the following differential equations:

$$\begin{aligned}\frac{dE_L}{dt} &= \beta_L M - \mu_{E_L} \left(1 + \frac{E_L + L_L}{K_L}\right) E_L - \frac{E_L}{d_{E_L}} \\ \frac{dL_L}{dt} &= \frac{E_L}{d_{E_L}} - \mu_{L_L} \left(1 + \gamma_L \left(\frac{E_L + L_L}{K_L}\right)\right) L_L - \frac{L_L}{d_{L_L}} \\ \frac{dP_L}{dt} &= \frac{L_L}{d_{L_L}} - \mu_{P_L} P_L - \frac{P_L}{d_{P_L}}\end{aligned}$$

$$\frac{dS_M}{dt} = \frac{P_L}{2d_{P_L}} - \lambda_M S_M - \mu_M S_M$$

$$\frac{dE_M}{dt} = \lambda_M S_M - \lambda_M(t - \tau_M) S_M(t - \tau_M) P_M - \mu_M E_M$$

$$\frac{dI_M}{dt} = \lambda_M(t - \tau_M) S_M(t - \tau_M) P_M - \mu_M I_M$$

Mortalities in larval stages are density-dependent, which increase with increasing population size. Both μ_{E_L} and μ_{L_L} are mortality rates at very low densities, K_L is the environmental carrying capacity, and γ_L is a factor that gives differential effects on mortality in late and early instar larvae. In adult mosquito stages, $P_M = \exp(-\mu_M \tau_M)$ is the probability that a mosquito survives the period between infection until sporozoites appear in the salivary glands (τ_M , the extrinsic incubation period, EIP), μ_M is the mortality rate of adult mosquitoes, and λ_M is the force of infection on mosquito, which is the sum of contributions from all human infectious states:

$$\lambda_M = \frac{\alpha}{\omega} \sum_i \sum_j \zeta_j \psi_i (C_D D_{i,j}(t - \tau_G) + C_T T_{i,j}(t - \tau_G) + C_A A_{i,j}(t - \tau_G) + C_U U_{i,j}(t - \tau_G))$$

where α is the rate at which a mosquito takes a human blood meal, ω is the normalising constant for the biting rates over ages ($\omega = \int_0^\infty \eta(a) \psi(a) da$), with a population distribution of $\eta(a)$. C_D , C_T , C_A , and C_U are parameters specifying the relative infectiousness of different infectious states in humans towards mosquitoes, which belongs to untreated clinical disease, treated clinical disease, patent asymptomatic, and sub-patent asymptomatic states, respectively.

For each mosquito species modelled, the human adult EIR is given by:

$$\varepsilon_0^v(t) = \frac{\alpha^v I_M^v}{\omega}$$

The overall EIR, if, for example, there are three mosquito species modelled is given by:

$$\varepsilon_0 = \varepsilon_0^1 + \varepsilon_0^2 + \varepsilon_0^3$$

Incorporation of vector control in the model

Vector control methods incorporated in the model are LLINs and IRS. Those vector control methods affect the transmission cycle in four different ways:

- 1) increasing the overall mosquito death rate;
- 2) lengthen the feeding or gonotrophic cycle of the mosquito;
- 3) changing the proportion of bites taken on protected and unprotected humans; and

- 4) changing the proportion of bites taken on humans relative to animals (the human blood index, HBI).

The model assumes that there are five different outcomes when a mosquito attempt to feed:

- 1) it bites a non-human host;
- 2) it is killed by the LLIN before it bites;
- 3) it is killed by IRS after it bites;
- 4) it successfully feeds and survives after that feeding attempt; and
- 5) it is repelled without feeding, either through the action of LLIN or IRS.

Repelled mosquitoes will go to find alternative blood meal sources ('repeating' process). The flow chart of the feeding attempt is shown in **Figure S1.2**. During a single feeding attempt, the probability of a mosquito successfully feeding is:

$$W = 1 - Q_0 + Q_0 \sum_i \pi_i w_i$$

The probability of a mosquito repelled without feeding is given by:

$$Z = Q_0 \sum_i \pi_i z_i$$

where Q_0 is the HBI in the absence of any intervention, π_i is the proportion of bites on humans that person i receives, w_i is the probability of a mosquito feeding on person i and surviving during a single feeding attempt, and z_i is the probability of a mosquito being repelled without feeding after an attempt to feed on person i in a single attempt.

The mosquito feeding rate, f_R , is defined as:

$$f_R = \frac{1}{\delta_1 + \delta_2}$$

where δ_1 and δ_2 are the time spent looking for a blood meal and resting between feeds, respectively. δ_2 is assumed not to be affected by interventions, while δ_1 is affected by the repellency effect of interventions, increasing the value to:

$$\delta_1 = \frac{\delta_{10}}{1 - Z}$$

where δ_{10} is the default value when there are no interventions. The probabilities of a mosquito surviving the periods of feeding (p_1) and resting (p_2) when there are no interventions are given by:

$$p_{10} = \exp(-\mu_0 \delta_{10}), p_2 = \exp(-\mu_0 \delta_2)$$

where μ_0 is the natural mortality rate of an adult mosquito. Accounting for vector controls, p_2 is unchanged, while p_1 increases to:

$$p_1 = \frac{p_{10}W}{1 - Zp_{10}}$$

The probability of a mosquito surviving an entire feeding and resting cycle is p_1p_2 . The mosquito mortality rate, μ_M , can be calculated as:

$$p_1p_2 = \exp(-\mu_M/f_R)$$

$$\mu_M = -f_R \log(p_1p_2)$$

Accounting for the presence of interventions, the probability of surviving the extrinsic incubation period (P_M) also changes as μ_M changes.

The probability that a feeding cycle ends with a successful blood meal on person i is given by:

$$q_i = p_{10}(Q_0\pi_iw_i + Zq_i)$$

$$q_i = \frac{p_{10}Q_0\pi_iw_i}{1 - Zp_{10}}$$

On the other hand, the probability that a feeding cycle ends with a blood meal on an animal is given by:

$$q_A = p_{10}(1 - Q_0 + Zq_A)$$

$$q_i = \frac{p_{10}(1 - Q_0)}{1 - Zp_{10}}$$

Therefore, the proportion of successful bites on humans is:

$$Q = 1 - \frac{q_A}{q_A + \sum_i q_i} = 1 - \frac{(1 - Q_0)}{(1 - Q_0) + Q_0 \sum_i \pi_i w_i} = 1 - \frac{(1 - Q_0)}{W}$$

Hence, the biting rate on humans is:

$$\alpha = Qf_R$$

The rate at which a specific mosquito species bite person i is:

$$\theta_i = \frac{\alpha\pi_iw_i}{\sum_i \pi_iw_i}$$

When IRS is used, mosquitoes may bite a person before dying after exposure to lethal insecticide when resting on the walls. To account for that, in the force of infection on humans, the biting rate on each person needs to be inflated by a factor of $\frac{y_i}{w_i}$, where y_i is the probability of a mosquito successfully feeding on person i during a single attempt. Therefore, the effective biting rate related to transmission towards humans is:

$$\tilde{\theta}_i = \frac{\alpha \pi_i y}{\sum_i \pi_i w_i}$$

Therefore, the EIR for each person i for each mosquito species is $\tilde{\theta}_i I_M$. Therefore, the total EIR from all mosquito species present in the region is the sum of all EIR contributions of each species.

The values of y_i , w_i , and z_i vary according to the presence of vector controls, accounting for the mechanisms by which each vector control (i.e., LLIN and IRS) kills or repels mosquitoes. Let $\theta_I(t)$ be the rate at which person i , who is indoors at hour t , is bitten, and $\theta_O(t)$ be the equivalent of the person outdoors. Given the proportions of humans who are indoors at time t ($p_I(t)$) and outdoors at time t ($p_O(t)$), the proportion of bites taken on humans while indoors is given by:

$$\phi_I = \frac{\sum_t p_I(t) \theta_I(t)}{\sum_t ((1 - p_I(t)) \theta_O(t) + p_I(t) \theta_I(t))}$$

While the proportion of bites taken on humans while in bed is given by:

$$\phi_B = \frac{\sum_t p_B(t) \theta_I(t)}{\sum_t ((1 - p_I(t)) \theta_O(t) + p_I(t) \theta_I(t))}$$

Once a mosquito enters a house to feed, there are three possibilities for what it would do: 1) repeat the feeding attempt (r), 2) feed successfully (s), or 3) die (d). Let r_N , s_N , and d_N as repetition, successful feeding attempt, and death probabilities caused by an LLIN, and r_S , s_S , and d_S as repetition, successful feeding attempt, and death probabilities due to IRS. **Figure S1.3** shows how each intervention protects humans by either killing or repelling mosquitoes and their corresponding probabilities. Death from LLINs is assumed to occur before feeding, while death from IRS is assumed to occur after feeding.

When no vector controls are in place, $y_i = w_i = 1$ and $z_i = 0$. However, when at least one vector control is in place, those probabilities are calculated using formulas defined in **Table S1.1**. Furthermore, the model also accounts for the waning efficacy of the insecticide contained in IRS and LLINs. For IRS, the repellency and mortality effects start at the optimum values (r_{s0} and d_{s0} , respectively) from the start of spraying and then decrease at a constant rate (γ_S) over time. The effectiveness of IRS also depends on the endophilic degree of the mosquito (the proportion of mosquitoes resting on the walls long enough for the killing effect of the IRS kicks in), χ . Hence, at time t after the IRS has been applied, the IRS parameters are calculated by:

$$r_S(t) = r_{s0} \exp(-t\gamma_S)$$

$$d_S(t) = \chi d_{s0} \exp(-t\gamma_S)$$

$$s_S(t) = 1 - d_S$$

For LLIN, the repellency and mortality effects start from the maximum r_{N0} and d_{N0} , respectively. The repellency effect then decreases up to a non-zero level, r_{NM} , which reflects the level of protection provided by a net that no longer has any insecticidal effect and potentially some holes. Finally, the mortality effect of LLIN decreases at a constant rate γ_N . Hence, at time t after the nets were distributed, the LLIN parameters are calculated by:

$$r_N(t) = (r_{N0} - r_{NM}) \exp(-t\gamma_N) + r_{NM}$$

$$d_N(t) = d_{N0} \exp(-t\gamma_N)$$

$$s_N(t) = 1 - r_N - d_N$$

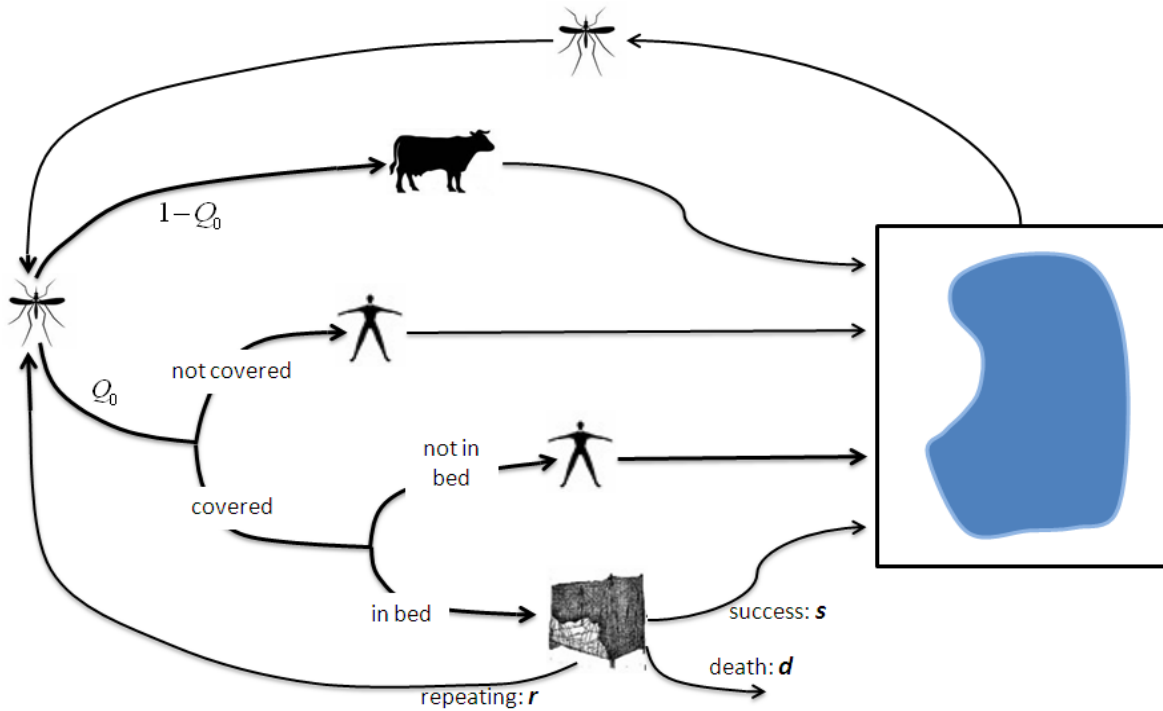


Figure S1.2. Flow chart of the mosquito feeding cycle accounting for the presence of humans and animals as blood meal sources, and whether the human population is covered with intervention or not. The figure was reproduced from Griffin et al. (Griffin et al., 2010).

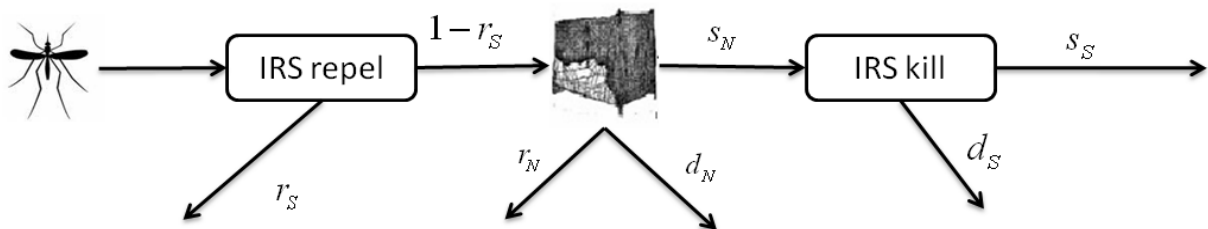


Figure S1.3. Flow chart of the modelled mechanisms of protection via the usage of LLIN and IRS. The figure was reproduced from Griffin et al. (Griffin et al., 2010).

Table S1.1. Probabilities of successful feeding and surviving, biting, and repelled for combinations of LLIN and IRS interventions

	IRS only	LLINs only	IRS and LLINs
Probability of successful feeding and surviving (w_i)	$1 - \phi_I + \phi_I(1 - r_S)s_S$	$1 - \phi_B + \phi_B s_N$	$1 - \phi_I + \phi_B(1 - r_S)s_N s_S + (\phi_I - \phi_B)(1 - r_S)s_S$
Probability of successful biting (y_i)	$1 - \phi_I + \phi_I(1 - r_S)$	$1 - \phi_B + \phi_B s_N$	$1 - \phi_I + \phi_B(1 - r_S)s_N + (\phi_I - \phi_B)(1 - r_S)$
Probability of repellency (z_i)	$\phi_I r_S$	$\phi_B r_N$	$\phi_B(1 - r_S)r_N + \phi_I r_S$

Chapter 3 supplementary materials

Tables

Table S3.1. List of districts, districts' indexes, and probability of disease severity and outcomes for the metapopulation model.

Index no.	District	Province	$p_{hosp,i}$	$p_{critical hosp,i}$	$p_{death non critical,i}$
1	Jakarta	Jakarta	0.029	0.185	0.054
2	Outside Java	Outside Java	0.027	0.195	0.058
3	Bogor	West Java	0.026	0.190	0.056
4	Sukabumi	West Java	0.031	0.216	0.065
5	Cianjur	West Java	0.031	0.212	0.064
6	Bandung	West Java	0.028	0.201	0.060
7	Garut	West Java	0.030	0.219	0.067
8	Tasikmalaya	West Java	0.034	0.228	0.070
9	Ciamis	West Java	0.039	0.234	0.072
10	Kuningan	West Java	0.036	0.233	0.072
11	Cirebon	West Java	0.030	0.209	0.063
12	Majalengka	West Java	0.036	0.229	0.070
13	Sumedang	West Java	0.036	0.234	0.073
14	Indramayu	West Java	0.033	0.210	0.063
15	Subang	West Java	0.035	0.224	0.069
16	Purwakarta	West Java	0.029	0.206	0.061
17	Karawang	West Java	0.030	0.200	0.059
18	Bekasi	West Java	0.025	0.177	0.051
19	Bandung Barat	West Java	0.030	0.214	0.065
20	Pangandaran	West Java	0.038	0.231	0.071
21	Kota Bogor	West Java	0.029	0.195	0.058
22	Kota Sukabumi	West Java	0.031	0.212	0.064
23	Kota Bandung	West Java	0.030	0.199	0.059
24	Kota Cirebon	West Java	0.031	0.201	0.060
25	Kota Bekasi	West Java	0.026	0.165	0.047
26	Kota Depok	West Java	0.027	0.176	0.051
27	Kota Cimahi	West Java	0.028	0.191	0.056
28	Kota Tasikmalaya	West Java	0.031	0.207	0.062

29	Kota Banjar	West Java	0.036	0.227	0.070
30	Cilacap	Central Java	0.035	0.232	0.072
31	Banyumas	Central Java	0.036	0.236	0.073
32	Purbalingga	Central Java	0.035	0.233	0.072
33	Banjarnegara	Central Java	0.035	0.229	0.071
34	Kebumen	Central Java	0.037	0.247	0.078
35	Purworejo	Central Java	0.040	0.254	0.081
36	Wonosobo	Central Java	0.035	0.230	0.071
37	Magelang	Central Java	0.036	0.236	0.073
38	Boyolali	Central Java	0.038	0.248	0.078
39	Klaten	Central Java	0.039	0.249	0.079
40	Sukoharjo	Central Java	0.035	0.233	0.072
41	Wonogiri	Central Java	0.044	0.260	0.084
42	Karanganyar	Central Java	0.036	0.235	0.073
43	Sragen	Central Java	0.038	0.244	0.077
44	Grobogan	Central Java	0.035	0.230	0.071
45	Blora	Central Java	0.037	0.240	0.075
46	Rembang	Central Java	0.034	0.225	0.069
47	Pati	Central Java	0.036	0.233	0.072
48	Kudus	Central Java	0.031	0.206	0.062
49	Jepara	Central Java	0.032	0.219	0.067
50	Demak	Central Java	0.030	0.210	0.063
51	Semarang	Central Java	0.035	0.234	0.073
52	Temanggung	Central Java	0.036	0.231	0.071
53	Kendal	Central Java	0.033	0.221	0.067
54	Batang	Central Java	0.033	0.217	0.066
55	Pekalongan	Central Java	0.031	0.217	0.066
56	Pemalang	Central Java	0.033	0.224	0.068
57	Tegal	Central Java	0.032	0.221	0.068
58	Brebes	Central Java	0.032	0.222	0.068
59	Kota Magelang	Central Java	0.036	0.229	0.071
60	Kota Surakarta	Central Java	0.033	0.220	0.067
61	Kota Salatiga	Central Java	0.033	0.227	0.070
62	Kota Semarang	Central Java	0.030	0.205	0.061
63	Kota Pekalongan	Central Java	0.030	0.202	0.060
64	Kota Tegal	Central Java	0.031	0.210	0.063
65	Kulon Progo	Yogyakarta	0.040	0.248	0.078
66	Bantul	Yogyakarta	0.035	0.232	0.072
67	Gunung Kidul	Yogyakarta	0.042	0.253	0.080
68	Sleman	Yogyakarta	0.033	0.223	0.068
69	Kota Yogyakarta	Yogyakarta	0.032	0.215	0.065
70	Pacitan	East Java	0.042	0.252	0.080
71	Ponorogo	East Java	0.041	0.247	0.078
72	Trenggalek	East Java	0.039	0.240	0.075
73	Tulungagung	East Java	0.038	0.237	0.074
74	Blitar	East Java	0.039	0.243	0.076
75	Kediri	East Java	0.036	0.231	0.071
76	Malang	East Java	0.036	0.228	0.070

77	Lumajang	East Java	0.036	0.222	0.068
78	Jember	East Java	0.035	0.224	0.068
79	Banyuwangi	East Java	0.037	0.230	0.071
80	Bondowoso	East Java	0.038	0.227	0.070
81	Situbondo	East Java	0.036	0.218	0.067
82	Probolinggo	East Java	0.034	0.217	0.066
83	Pasuruan	East Java	0.031	0.201	0.060
84	Sidoarjo	East Java	0.029	0.190	0.056
85	Mojokerto	East Java	0.033	0.211	0.063
86	Jombang	East Java	0.034	0.223	0.069
87	Nganjuk	East Java	0.037	0.231	0.072
88	Madiun	East Java	0.041	0.241	0.075
89	Magetan	East Java	0.043	0.251	0.080
90	Ngawi	East Java	0.040	0.236	0.074
91	Bojonegoro	East Java	0.037	0.229	0.071
92	Tuban	East Java	0.035	0.223	0.068
93	Lamongan	East Java	0.037	0.226	0.069
94	Gresik	East Java	0.031	0.201	0.059
95	Bangkalan	East Java	0.032	0.227	0.069
96	Sampang	East Java	0.029	0.211	0.064
97	Pamekasan	East Java	0.031	0.211	0.064
98	Sumenep	East Java	0.036	0.218	0.066
99	Kota Kediri	East Java	0.033	0.212	0.064
100	Kota Blitar	East Java	0.035	0.225	0.069
101	Kota Malang	East Java	0.031	0.211	0.064
102	Kota Probolinggo	East Java	0.032	0.207	0.062
103	Kota Pasuruan	East Java	0.030	0.203	0.060
104	Kota Mojokerto	East Java	0.033	0.209	0.063
105	Kota Madiun	East Java	0.037	0.227	0.070
106	Kota Surabaya	East Java	0.030	0.194	0.057
107	Kota Batu	East Java	0.034	0.221	0.068
108	Pandeglang	Banten	0.029	0.205	0.061
109	Lebak	Banten	0.028	0.194	0.057
110	Tangerang	Banten	0.025	0.172	0.049
111	Serang	Banten	0.027	0.185	0.054
112	Kota Tangerang	Banten	0.026	0.161	0.046
113	Kota Cilegon	Banten	0.026	0.167	0.048
114	Kota Serang	Banten	0.025	0.167	0.048
115	Kota Tangerang Selatan	Banten	0.027	0.169	0.048

Table S3.2. Model parameters descriptions and values for the metapopulation model.

Parameter	Symbol	Value	Description
Transmission rate	β_i	-	Calculated from $R_{0,i}$.
Basic reproduction number	$R_{0,i}$	-	Estimated from the maximum values of the smoothing spline

			models between mobility changes and $R_{t,funerals}$.
Relative changes in daily transmission rate	κ_i	-	The ratio between $R_{0,i}$ and daily estimated $R_{t,i}$ based on spline smoothing models.
Mean latent period	$1/\alpha$	4.6 days	Estimated as 5.1 days (Lauer et al., 2020) with 0.5 days accounted as a pre-symptomatic period of infectiousness.
Mean duration of infectiousness of mild infections	$1/\gamma_1$	2.1 days	0.5 days infectiousness period prior to symptoms included which in combination with mean duration of severe illness gives a mean serial interval of 6.75 days (Bi et al., 2020b).
Mean duration of infectiousness of severe infections	$1/\gamma_2$	4.5 days	Mean onset to admission to hospital of 4 days, as used in the <i>squire</i> model (Walker et al., 2020), based on unpublished analysis of data from the ICNARC study (Intensive Care National Audit & Research Centre, 2020) and includes 0.5 days of infectiousness prior to symptoms.
Probability of having severe illness, needing hospitalisations	$p_{hosp,i}$	Table S3.1	For each district, the probability was calculated by running a full unmitigated epidemic using the <i>squire</i> package (Watson et al., 2020) The proportion of people needing hospitalisations were calculated based on the simulations.
Probability of needing critical care, if hospitalised	$p_{critical hosp,i}$	Table S3.1	For each district, the probability was calculated by running a full unmitigated epidemic using the <i>squire</i> package (Watson et al., 2020) The proportion of people needing critical care were calculated based on the simulations.
Probability of death of severe illness that does not need critical care	$p_{\text{death} \text{non critical},i}$	Table S3.1	For each district, the probability was calculated by running a full unmitigated epidemic using the <i>squire</i> package (Watson et al., 2020). The proportion of who die from non-critical severe illness

			were calculated based on the simulations.
Probability of death of severe illness that needs critical care	$p_{death critical,i}$	0.5	Probability of death from severe illness needing critical care based on the data of the ICNARC study in the UK (Intensive Care National Audit & Research Centre, 2020).

Figures

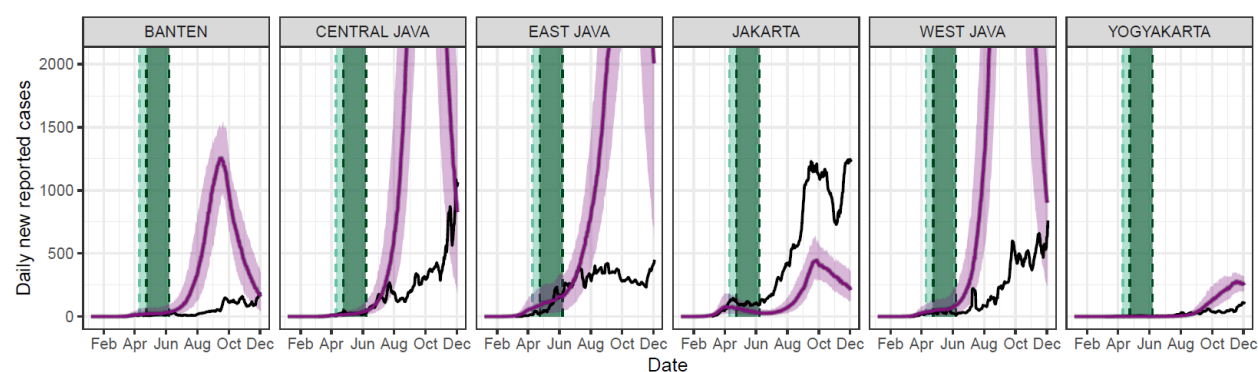


Figure S3.1. Comparison of model simulations and observed daily new reported cases from COVID-19. Coloured lines and their shaded areas denote model simulation outputs with their respective uncertainties (95% level). Black lines denote observed data. Light green shaded areas denote periods of PSBB, while the dark green shaded areas represent the period of Ramadan domestic travel restrictions.

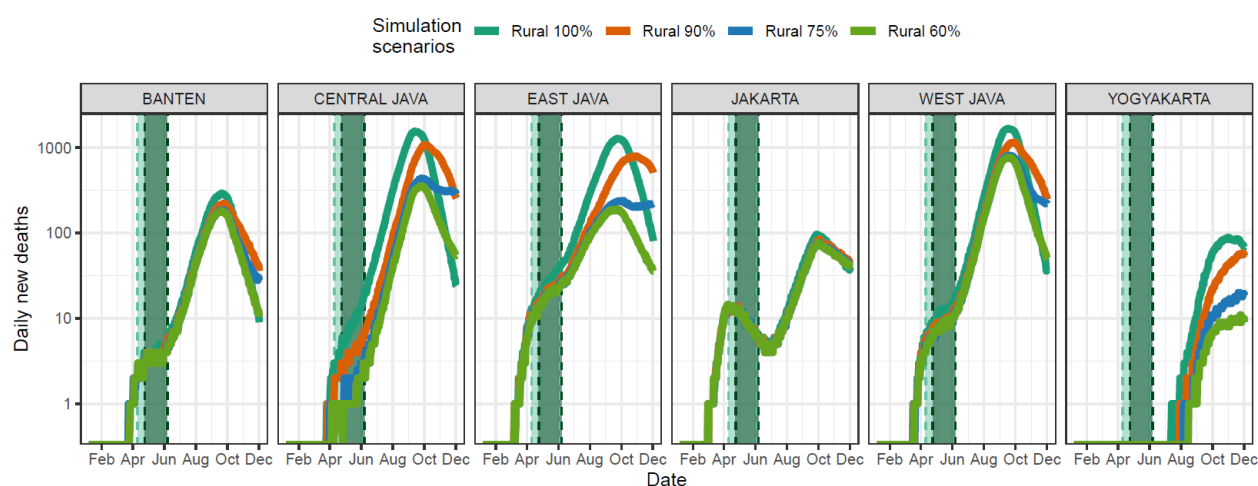


Figure S3.2. Simulated daily new COVID-19 deaths, comparing rural transmission scenarios at the province level. The detailed simulation scenarios are available in **Table 3.1**. Light green shaded areas denote periods of PSBB, while the dark green shaded areas represent the period of Ramadan domestic travel restrictions.

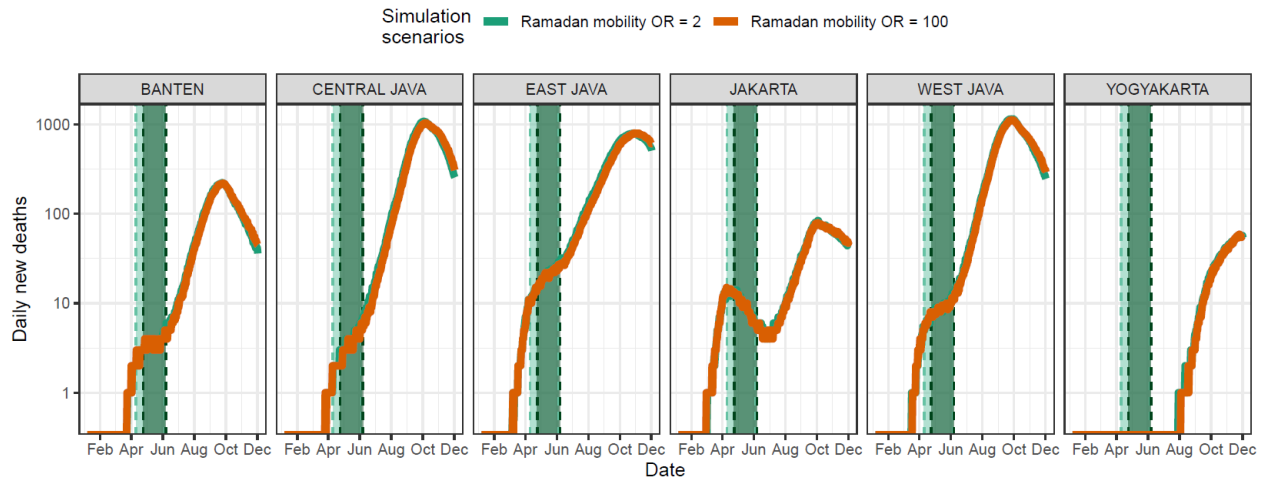


Figure S3.3. Sensitivity analysis of the assumed impact of between-district movement restrictions at the province level. Light green shaded areas denote periods of PSBB, while the dark green shaded areas represent the period of Ramadan domestic travel restrictions.

Chapter 4 supplementary materials

Tables

Table S4.1. Model parameters symbols, descriptions, and values for the SARS-CoV-2 age-structured model. Based on model parameters used in the squire package v0.5.8 (Watson et al., 2020).

Parameter	Symbol	Value	Description
Epidemiological parameters			
Transmission rate	β_i	-	Calculated from R_0 .
Basic reproduction number	R_0	-	Estimated from model fitting.
Mean latent period	$1/\alpha$	4.6 days	Estimated as 5.1 days (Q. Li et al., 2020; Linton et al., 2020) with 0.5 days accounted as a pre-symptomatic period of infectiousness.
Mean duration of mild infection	$1/\gamma_1$	2.1 days	0.5 days infectiousness period prior to symptoms included which in combination with mean duration of severe illness gives a mean serial interval of 6.75 days (Bi et al., 2020b).
Mean duration of severe infection prior to hospitalisation	$1/\gamma_2$	4.5 days	Mean onset to admission to hospital of 4 days, as used in squire model (Walker et al., 2020), based on unpublished analysis of data from the

			ICNARC study (Intensive Care National Audit & Research Centre, 2020) and includes 0.5 days of infectiousness prior to symptoms.
Mean duration of hospitalisation for non-critical cases if receiving treatment and survive	$1/\gamma_{3,1,1}$	9 days	Median values from various studies (N. J. L. Haw et al., 2020; Hawryluk et al., 2020; Oliveira et al., 2021; Sreevalsan-Nair et al., 2020)
Mean duration of hospitalisation for non-critical cases if receiving treatment and die	$1/\gamma_{3,1,0}$	9 days	Median values from various studies (N. J. L. Haw et al., 2020; Hawryluk et al., 2020; Oliveira et al., 2021; Sreevalsan-Nair et al., 2020)
Mean duration in intensive care unit (ICU)/critical care if survive	$1/\gamma_{4,1,1}$	14.8 days	Mean critical care duration of 13.3 days (Pritchard et al., 2020) with ratio of duration in critical care if die: duration in critical care if survive = 0.75 and probability of survival in the critical care = 60.1% (Intensive Care National Audit & Research Centre, 2020)
Mean duration in ICU if die	$1/\gamma_{4,1,0}$	11.1 days	Mean critical care duration of 13.3 days (Pritchard et al., 2020) with ratio of duration in critical care if die: duration in critical care if survive = 0.75 and probability of survival in the critical care = 60.1% (Intensive Care National Audit & Research Centre, 2020)
Mean duration in recovery after ICU	$1/\gamma_5$	3.4 days	Based on unpublished analysis of data from the ICNARC study (Intensive Care National Audit & Research Centre, 2020)
Mean duration of hospitalisation for non-critical cases if does not receive treatment and survive	$1/\gamma_{3,0,1}$	4.5 days	Assumed

Mean duration of hospitalisation for non-critical cases if does not receive treatment and die	$1/\gamma_{3,0,0}$	4.5 days	Assumed
Mean duration of hospitalisation if requiring ICU but does not receive it and survive	$1/\gamma_{4,0,1}$	7.4 days	Assumed
Mean duration of hospitalisation if requiring ICU but does not receive it and die	$1/\gamma_{4,0,0}$	1 day	Assumed
Probability of dying if requiring hospitalisation but does not receive treatment	μ	0.6	Assumed, informed by expert opinion
Probability of dying if requiring critical care but does not receive treatment	μ	0.95	Assumed, informed by expert opinion
Age-stratified parameters			
Probability of hospitalisation, given infection	$\phi_1(a)$	0 to 4 0.08% 5 to 9 0.12% 10 to 14 0.17% 15 to 19 0.23% 20 to 24 0.33% 25 to 29 0.46% 30 to 34 0.65% 35 to 39 0.91% 40 to 44 1.29% 45 to 49 1.81% 50 to 54 2.54% 55 to 59 3.58% 60 to 64 5.03% 65 to 69 7.08% 70 to 74 9.95% 75 to 79 14.0% 80+ 23.4%	(Salje et al., 2020)
Probability of requiring critical care, given hospitalisation	$\phi_2(a)$	0 to 4 18.1% 5 to 9 18.1% 10 to 14 18.1% 15 to 19 13.7% 20 to 24 12.2%	(Salje et al., 2020)

		25 to 29 12.3% 30 to 34 13.6% 35 to 39 16.1% 40 to 44 19.7% 45 to 49 24.2% 50 to 54 28.9% 55 to 59 32.7% 60 to 64 33.7% 65 to 69 30.9% 70 to 74 24.4% 75 to 79 16.0% 80+ 5.71%	
Proportion of hospital deaths occurring in ICU		0 to 4 80.0% 5 to 9 80.0% 10 to 14 80.0% 15 to 19 80.0% 20 to 24 80.0% 25 to 29 80.0% 30 to 34 80.0% 35 to 39 80.0% 40 to 44 80.0% 45 to 49 80.0% 50 to 54 80.0% 55 to 59 80.0% 60 to 64 80.0% 65 to 69 80.0% 70 to 74 80.0% 75 to 79 80.0% 80+ 80.0%	Assumed
Proportion of non-critical care cases dying	$\mu(a)$	0 to 4 1.30% 5 to 9 1.40% 10 to 14 1.60% 15 to 19 1.60% 20 to 24 1.80% 25 to 29 2.00% 30 to 34 2.30% 35 to 39 2.60% 40 to 44 3.00% 45 to 49 3.60% 50 to 54 4.20% 55 to 59 5.00% 60 to 64 5.60%	Calculated from infection fatality rate (IFR) in (Brazeau et al., 2020)

		65 to 69 6.00% 70 to 74 12.3% 75 to 79 18.4% 80+ 34.1%	
Proportion of critical care cases dying	$\mu(a)$	0 to 4 22.7% 5 to 9 25.2% 10 to 14 28.1% 15 to 19 41.3% 20 to 24 51.8% 25 to 29 57.3% 30 to 34 57.6% 35 to 39 54.3% 40 to 44 49.4% 45 to 49 44.7% 50 to 54 41.7% 55 to 59 41.1% 60 to 64 44.3% 65 to 69 53.9% 70 to 74 57.0% 75 to 79 64.3% 80+ 99.3%	Calculated from infection fatality rate (IFR) in (Brazeau et al., 2020)

Table S4.2. Estimated attack rate in each province in Java Island based on models fitted to confirmed or suspected deaths data on 2nd September 2020 and 7th December 2020.

Province	Death data type	Estimation date	Attack rate in percentage (95% CrI)
JAKARTA	Confirmed deaths	02-Sep	4.61 (4.22-5.20)
JAKARTA	Confirmed deaths	07-Dec	9.75 (8.74-11.49)
JAKARTA	Suspected deaths	02-Sep	18.43 (17.04-19.66)
JAKARTA	Suspected deaths	07-Dec	32.48 (30.09-34.63)
WEST JAVA	Confirmed deaths	02-Sep	0.20 (0.17-0.24)
WEST JAVA	Confirmed deaths	07-Dec	0.66 (0.54-0.75)
WEST JAVA	Suspected deaths	02-Sep	0.41 (0.36-0.49)
WEST JAVA	Suspected deaths	07-Dec	1.42 (1.25-1.67)
CENTRAL JAVA	Confirmed deaths	02-Sep	0.97 (0.85-1.13)
CENTRAL JAVA	Confirmed deaths	07-Dec	2.30 (1.96-2.81)
CENTRAL JAVA	Suspected deaths	02-Sep	2.41 (2.05-2.88)
CENTRAL JAVA	Suspected deaths	07-Dec	5.96 (5.10-6.98)
YOGYAKARTA	Confirmed deaths	02-Sep	0.41 (0.33-0.49)
YOGYAKARTA	Confirmed deaths	07-Dec	1.39 (1.05-1.68)
YOGYAKARTA	Suspected deaths	02-Sep	1.12 (0.92-1.37)
YOGYAKARTA	Suspected deaths	07-Dec	4.09 (3.33-5.24)

EAST JAVA	Confirmed deaths	02-Sep	2.13 (1.89-2.33)
EAST JAVA	Confirmed deaths	07-Dec	3.85 (3.39-4.40)
EAST JAVA	Suspected deaths	02-Sep	3.35 (2.89-3.83)
EAST JAVA	Suspected deaths	07-Dec	6.17 (5.46-7.38)
BANTEN	Confirmed deaths	02-Sep	0.34 (0.29-0.41)
BANTEN	Confirmed deaths	07-Dec	1.08 (0.90-1.34)
BANTEN	Suspected deaths	02-Sep	0.59 (0.50-0.68)
BANTEN	Suspected deaths	07-Dec	2.09 (1.75-2.51)

Figures

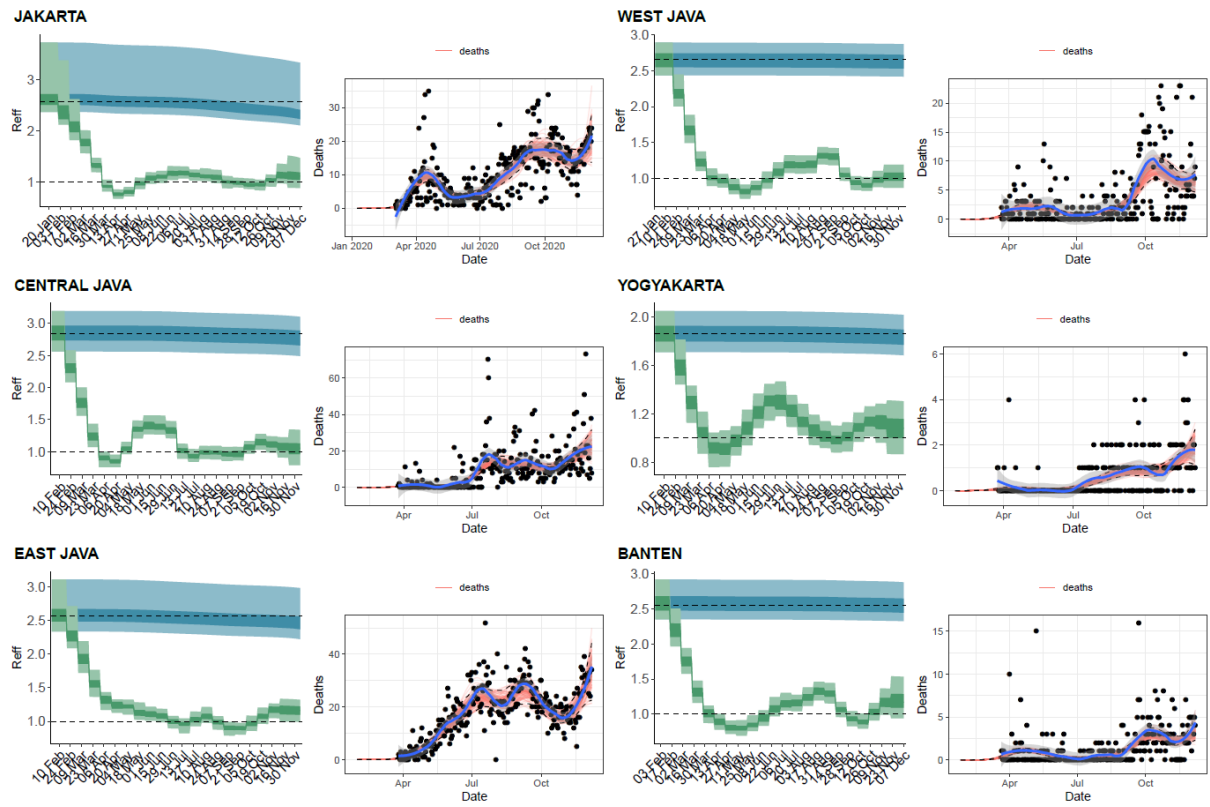


Figure S4.1. Province-level model calibrations to confirmed COVID-19 deaths and estimated R_c values.

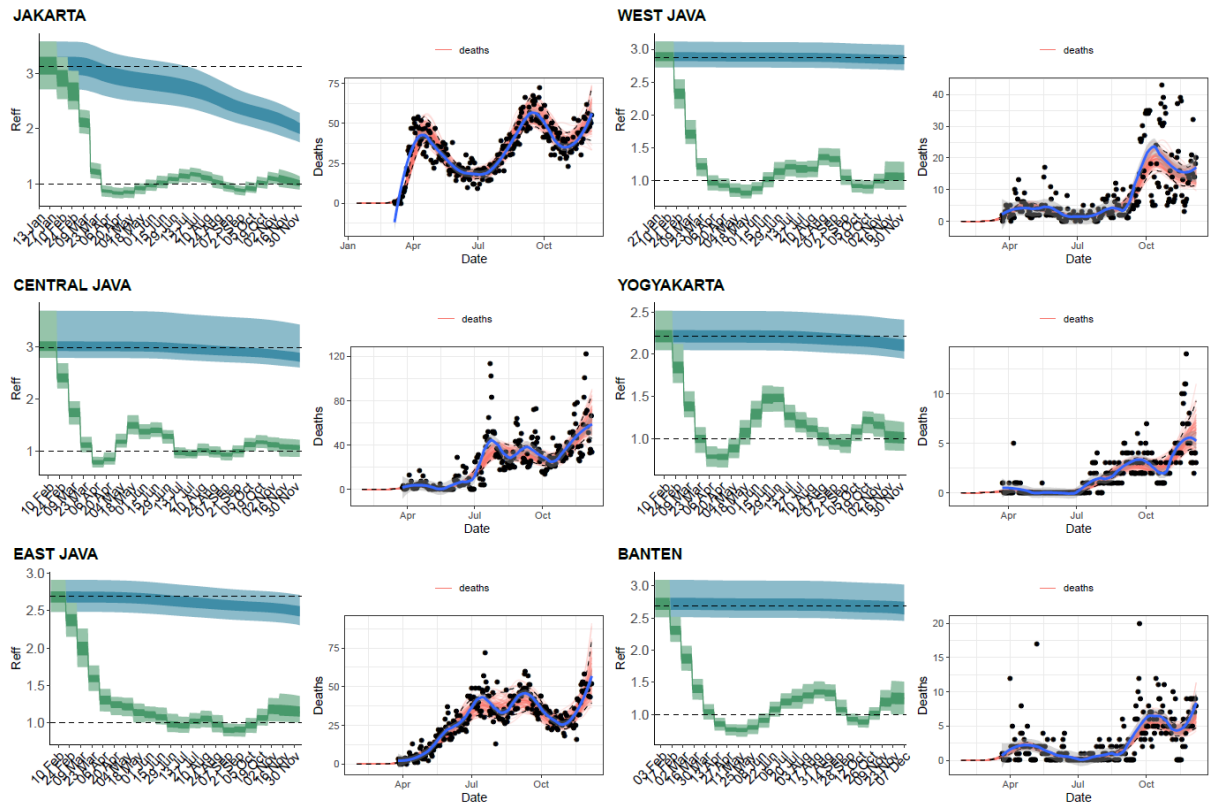


Figure S4.2. Province-level model calibrations to suspected COVID-19 deaths and estimated R_c values.

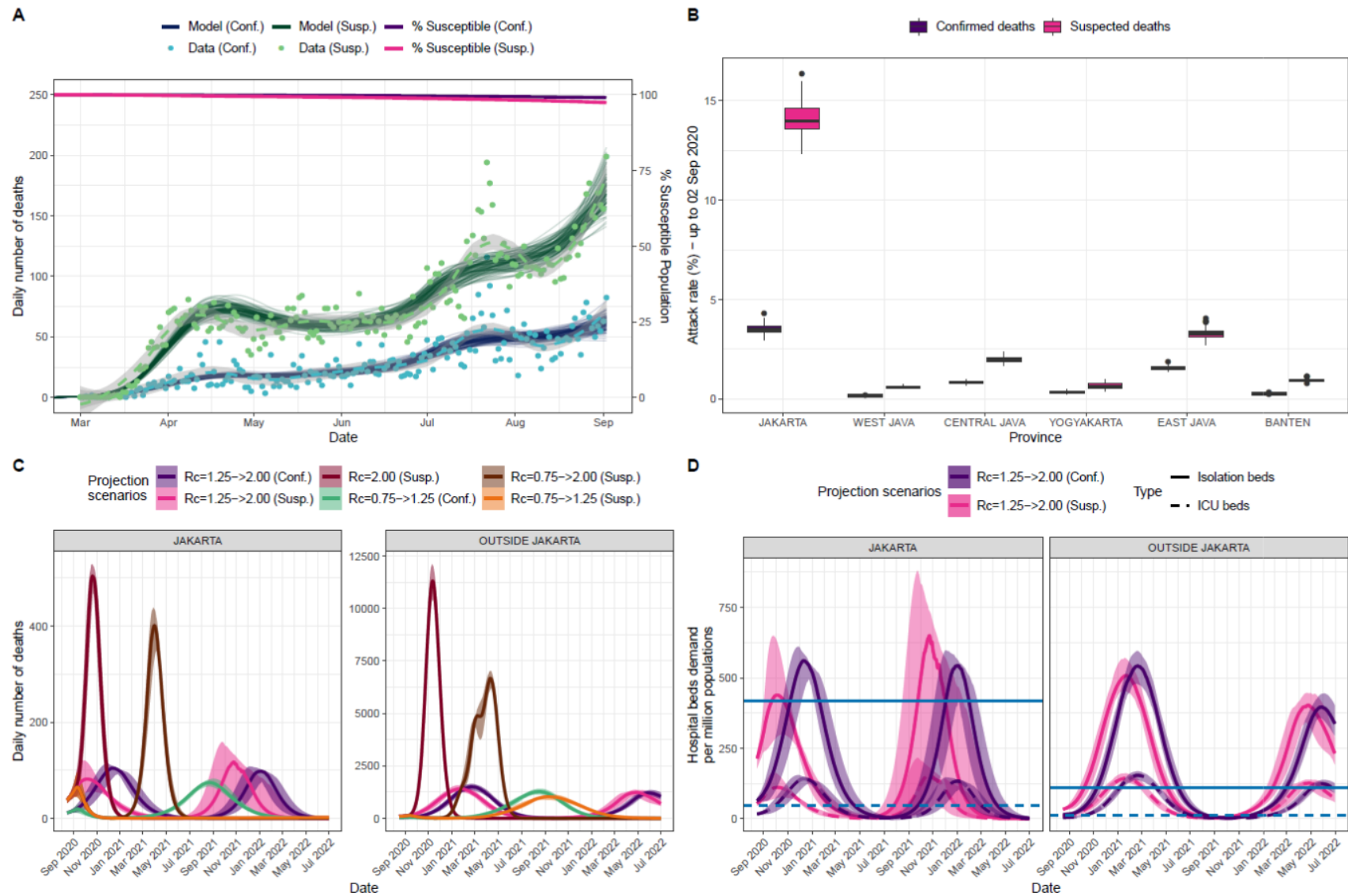


Figure S4.3. **A)** Model fitting to confirmed and suspected (both confirmed and probable) COVID-19-related deaths and inferred population susceptibility in Java; Green and blue dots show data on reported and suspected, respectively (where suspected includes augmented estimate of probable deaths in provinces outside Jakarta pre-May 13th), with associated median (lines) and 95% CrI (shaded areas) of model fits. **B)** Estimated province-level attack rates (cumulative proportion infected) based on confirmed (purple) and suspected COVID-19-related deaths. **C)** Projections of the daily number of deaths due to COVID-19 based on four different transmissibility scenarios. **D)** Healthcare demand projections in the form of isolation and ICU bed demands assuming the current level of transmission will continue in the future (with easing of control measures after the transmission reached a low level following the first peak in the graph). Projections are coloured according to whether they are based upon confirmed or suspected deaths to date and by projected R_c (with $R_c = x \rightarrow y$ representing $R_c = x$ for the immediate future and $R_c = y$, the level it returns to when the burden falls below seven deaths per week). Healthcare capacities are based on the current numbers of dedicated COVID-19 isolation beds and ICUs (Ministry of Health of the Republic of Indonesia, 2020b), not reflecting the total number of beds and ICUs in each province. The figure was reproduced from Djaafara et al. (Djaafara et al., 2020) (Figure 5).

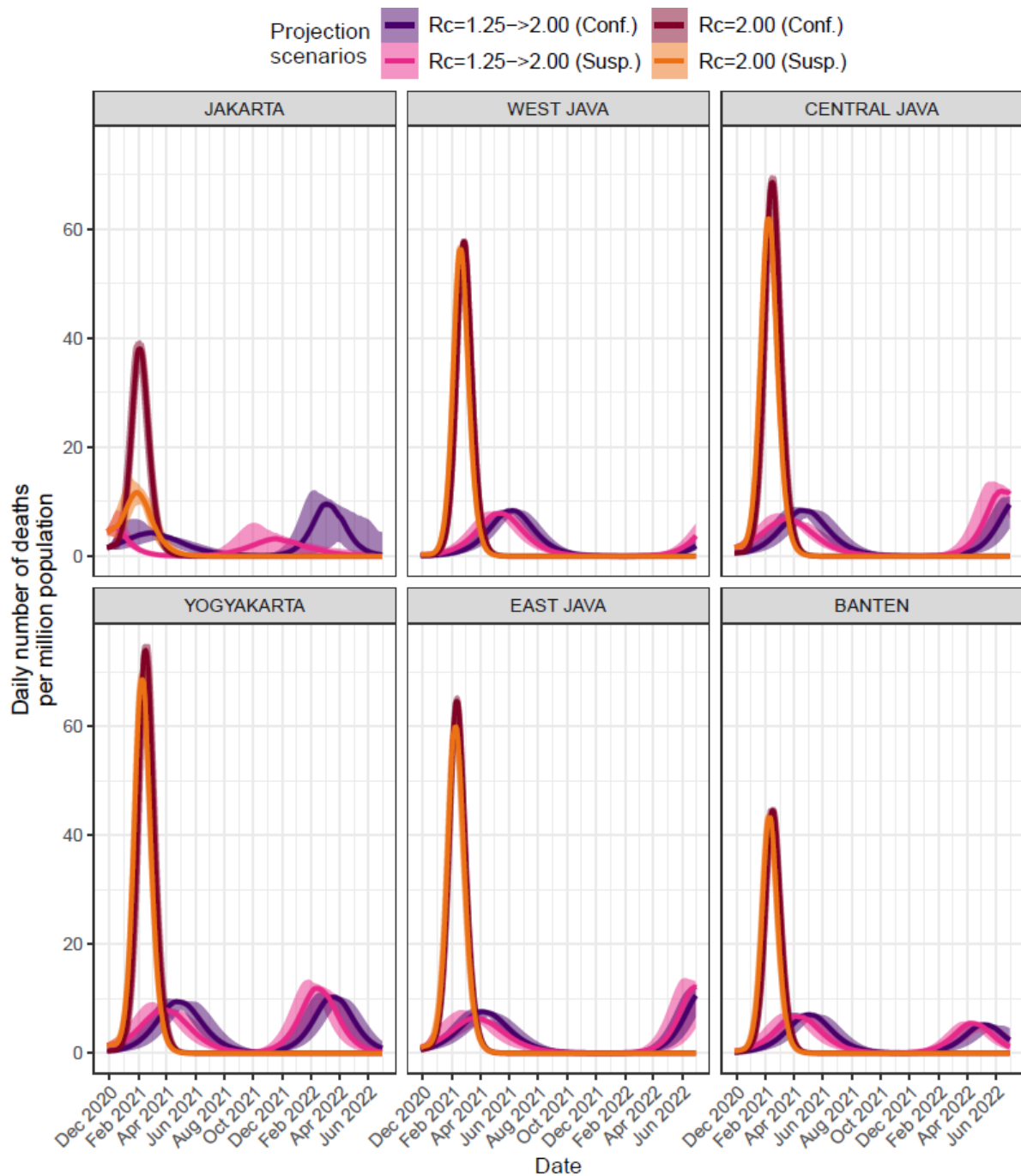


Figure S4.4. Projections of the daily number of deaths due to COVID-19 based on four different transmission scenarios as shown in Figure 5C in the main text but showing all provinces in Java. $R_c = 1.25$ represents the ‘current trajectory’ scenario.

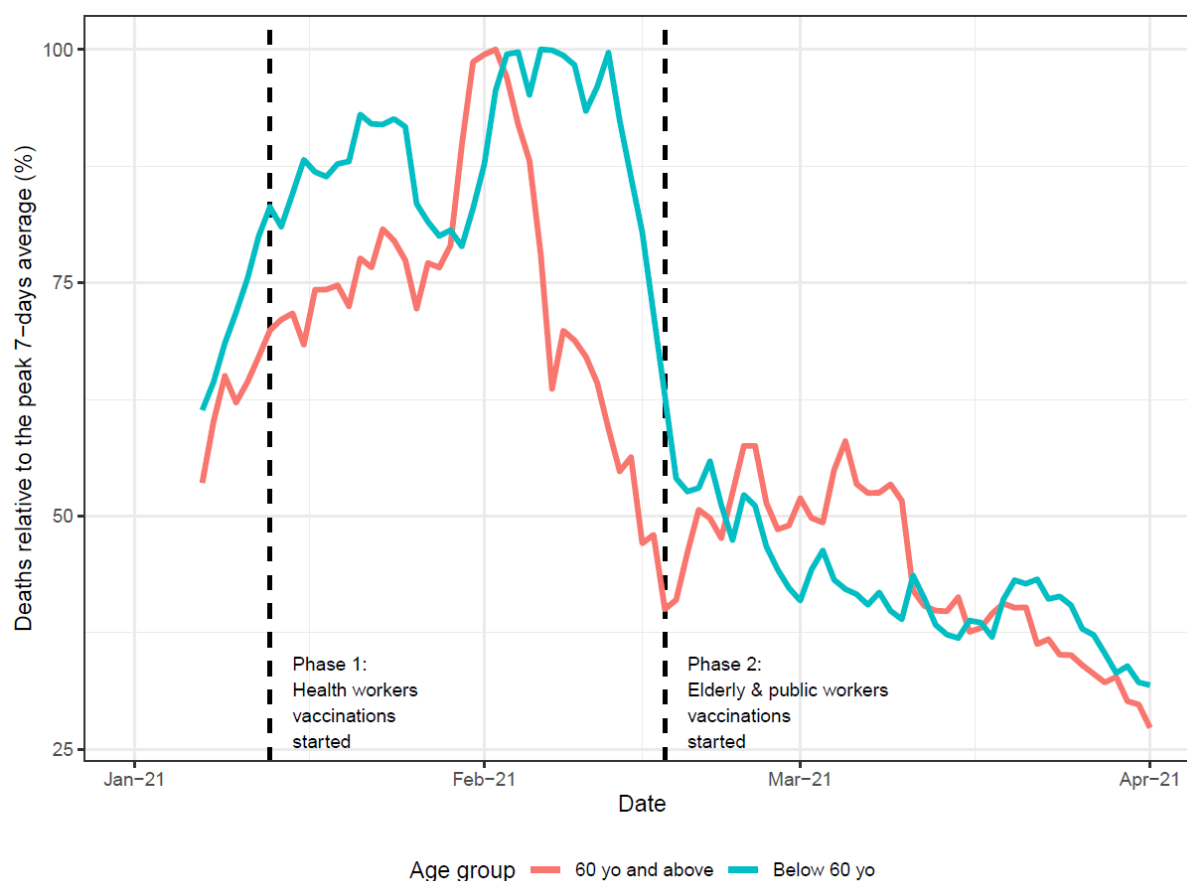


Figure S4.5. Daily COVID-19 deaths as a relative proportion (%) to the peak of the epidemic in early 2021 in Jakarta for the elderly (aged 60 years old and above) and non-elderly (aged below 60 years old). The 7-day moving average of the daily reported COVID-19 deaths was used for the calculations. Vaccinations for healthcare workers started on 13th January 2021. Vaccinations for elderly and public workers started on 17th February 2021. Data were obtained from the Jakarta Provincial Department of Health.

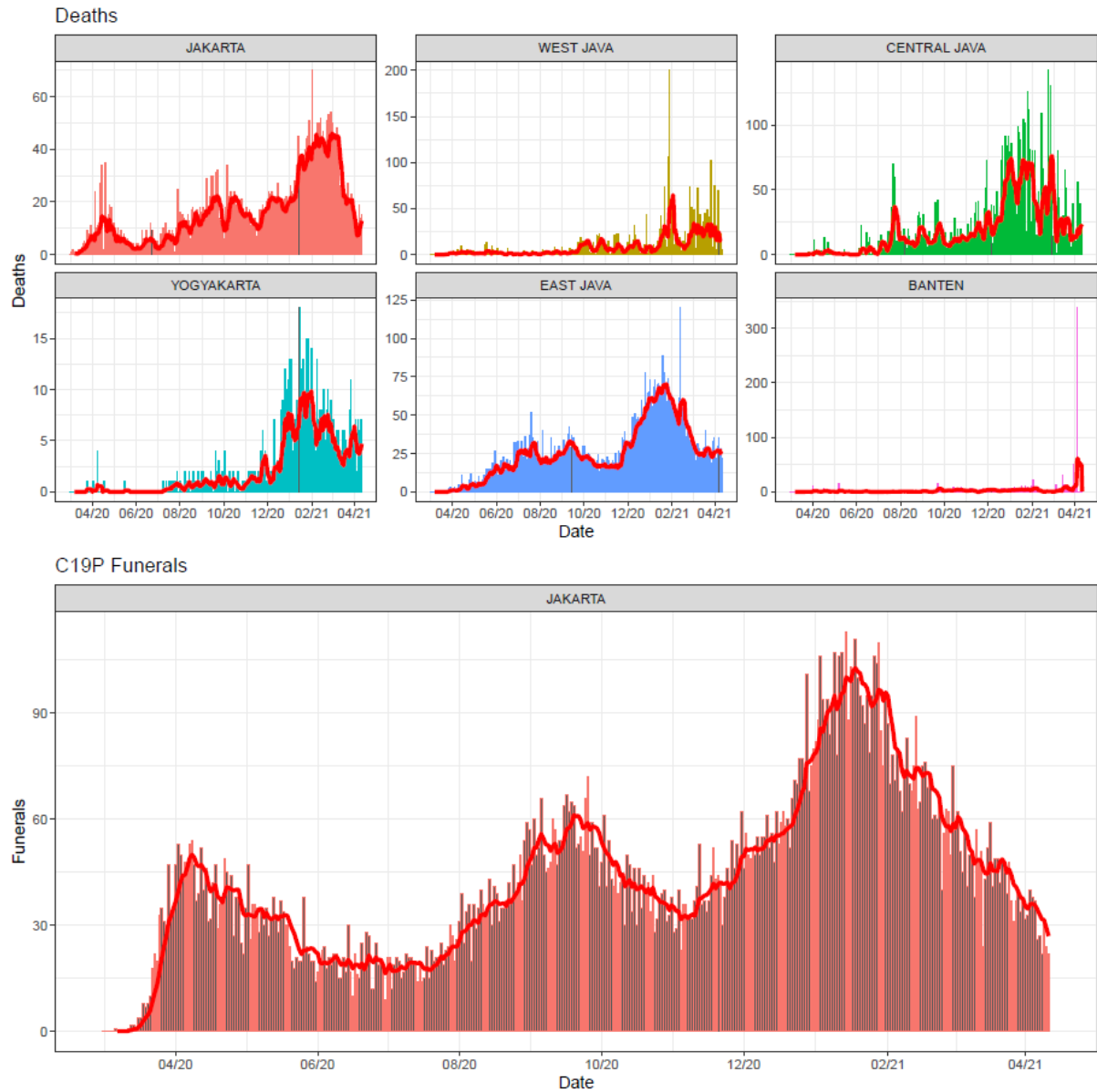


Figure S4.6. Daily reported COVID-19 deaths in all provinces in Jakarta up to 11th April 2021 and daily number of C19P funerals in Jakarta up to 11th April 2021. Red lines are the 7-day moving averages of the reported COVID-19 deaths/C19P funerals. Jakarta data were obtained from the Jakarta COVID-19 data monitoring website. Other provinces' data were obtained from KawalCOVI19 online spreadsheet.

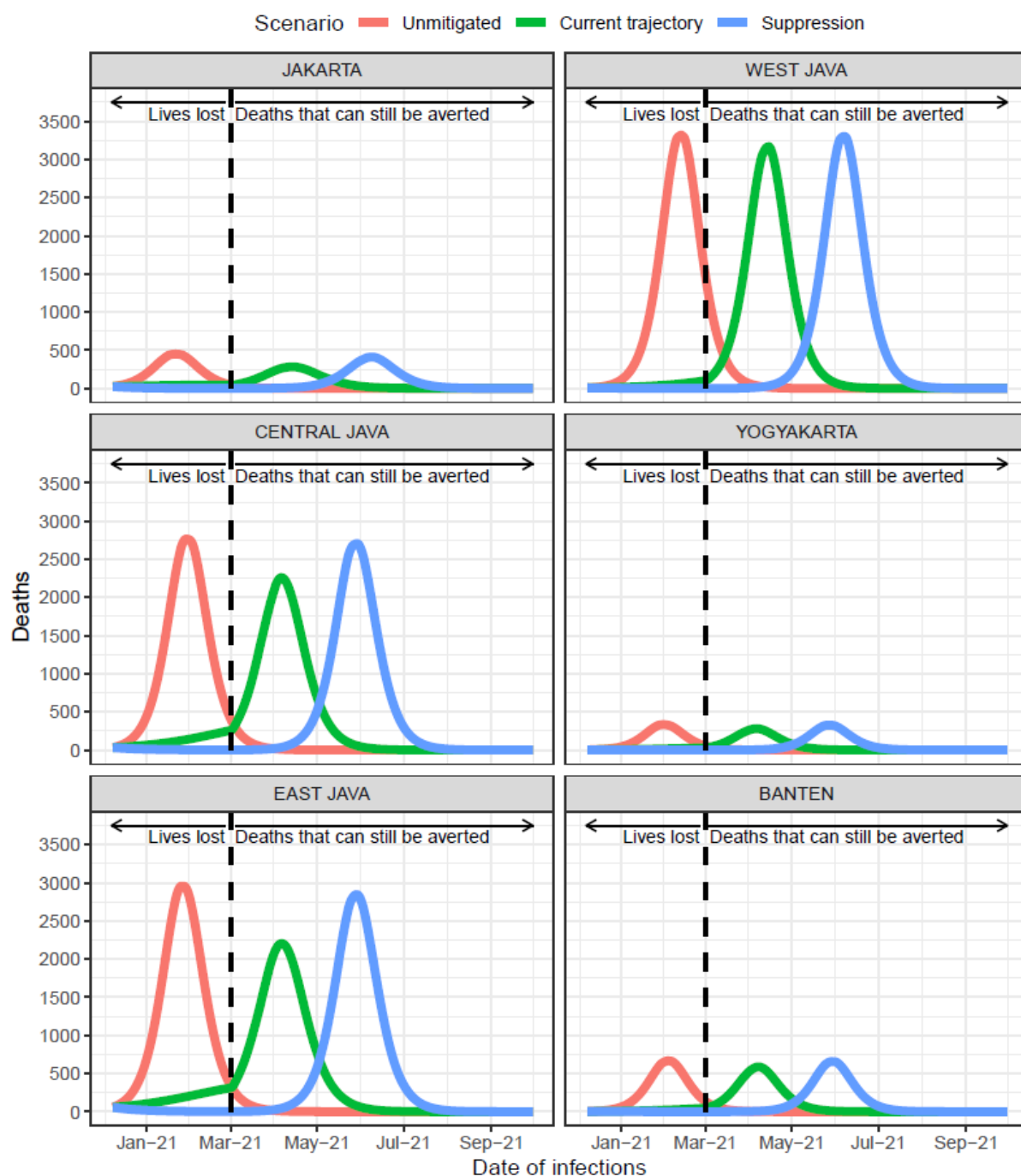


Figure S4.7. Illustrations of future scenario projections based on models fitted to confirmed COVID-19 deaths in each province in Java, subsequently ‘returning to normal’ on 1st March 2021. The Jakarta trajectories are similar to what are shown in **Figure 4.6A** of the main text.

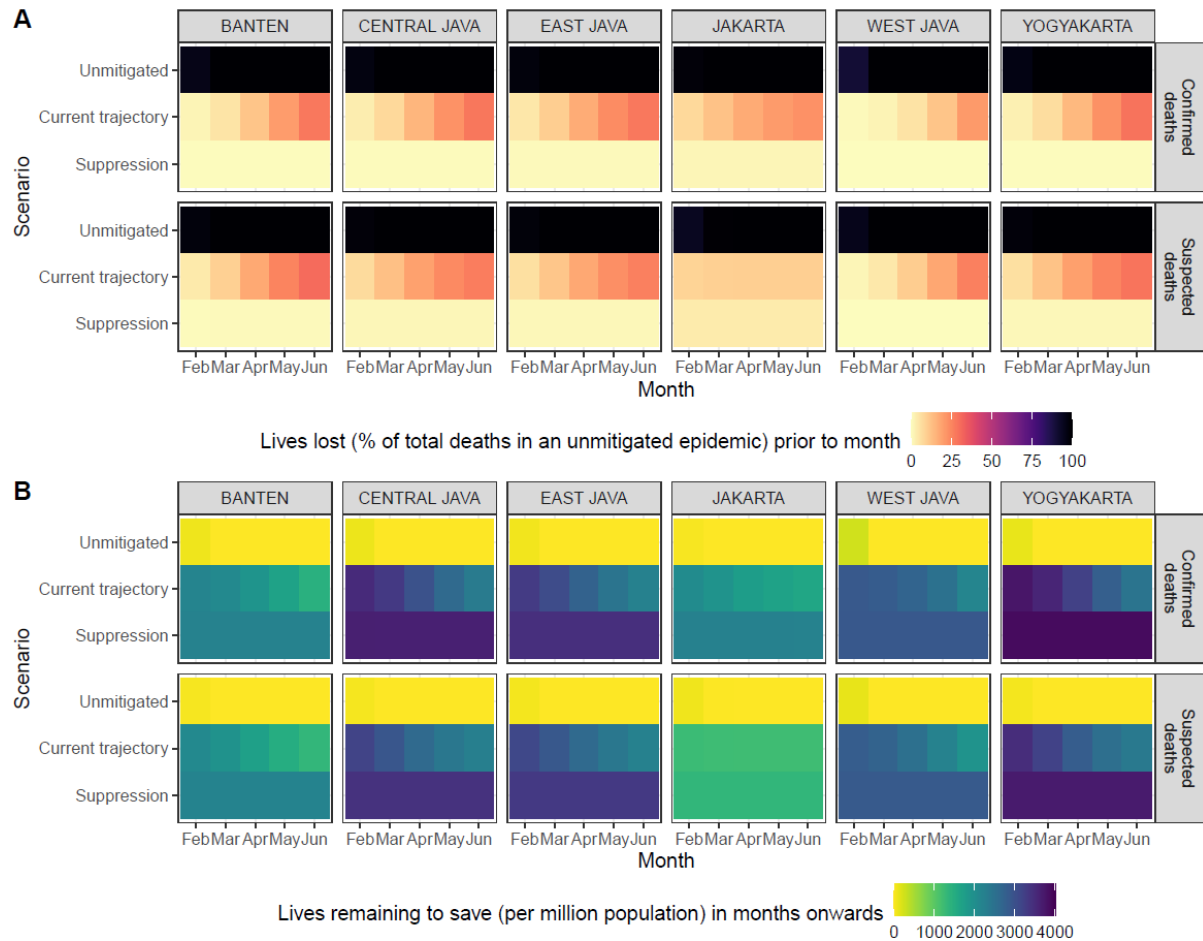


Figure S4.8. Additional analysis for projections of the number of lives lost and remaining to save (compared to Figure 6 in the main text), based on the assumptions of a higher reproduction number when ‘returning to normal’ and the epidemic is unmitigated ($R_c = 3.00$). **A**) Projected percentage of lives lost (compared to total deaths from an unmitigated epidemic scenario) prior to the start of each month from February to June 2021, based on each simulation scenario and model fitted to confirmed or suspected deaths in each province in Java. **B**) Projected number of lives remaining to be saved (or deaths that can still be averted) per million population after the start of each month from February to June 2021, based on each simulation scenario and model fitted to confirmed or suspected deaths in each province in Java.

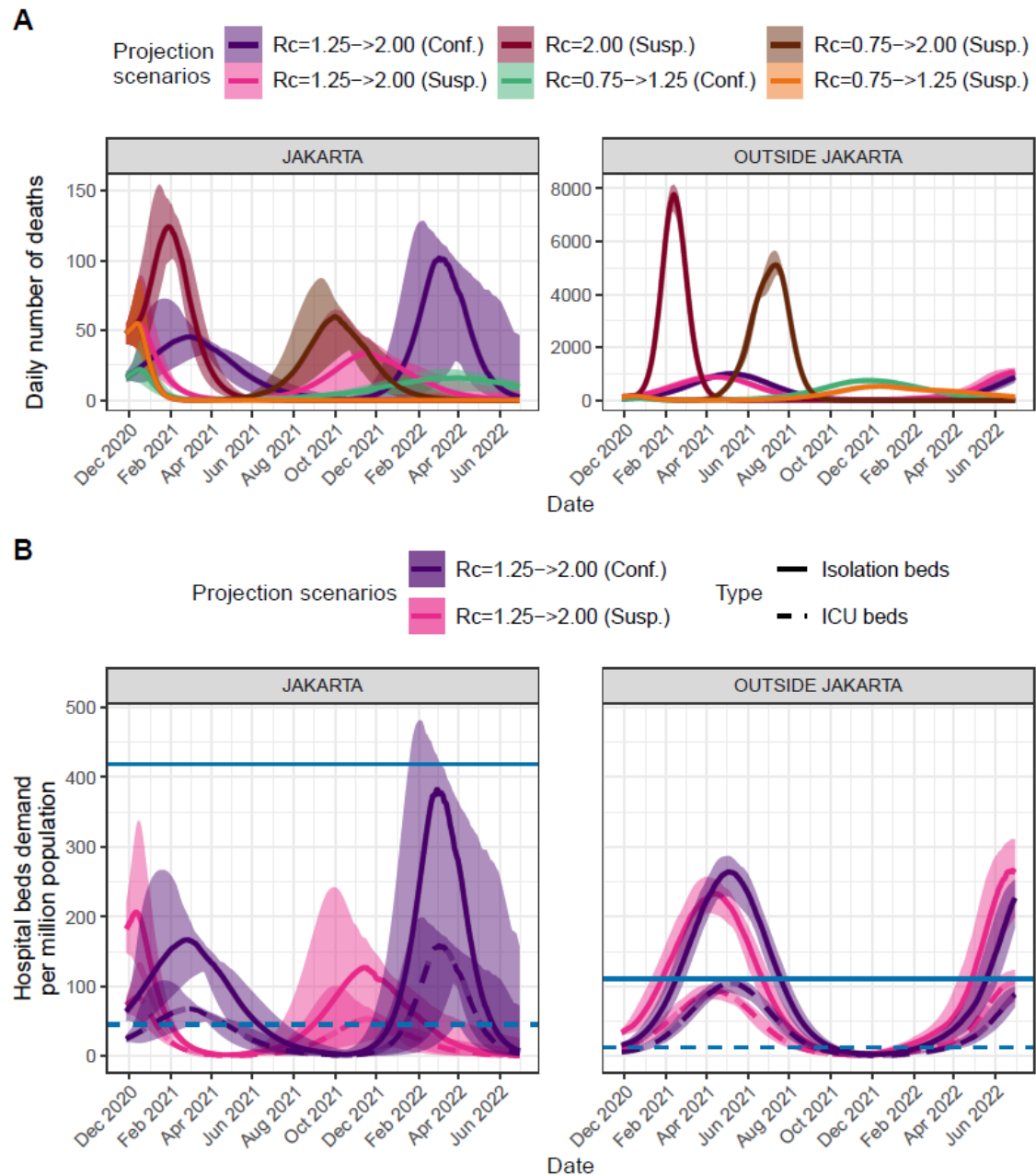


Figure S4.9. Future projections of deaths and healthcare demands based on various transmission scenarios. A) Projections of the daily number of deaths due to COVID-19; B) Healthcare demand projections in the form of isolation and ICU bed demands assuming the current level of transmission to continue in the future (with easing of control measures after the transmission reached a low-level following the first peak in the graph). Projections are coloured according to whether they are based upon confirmed or suspected deaths to date and by projected R_c (with $R_c = x \rightarrow y$ representing $R_c = x$ for the immediate future and $R_c = y$, the level it returns to when the burden falls below seven deaths per week). Healthcare capacities are based on the current numbers of dedicated COVID-19 isolation beds and ICUs, not reflecting the total number of beds and ICUs in each province.

Chapter 5 supplementary materials

Tables

Table S5.1. Variables contained in the routine surveillance data used in the analysis and their descriptions.

Variables	Descriptions
Total number of confirmatory malaria tests	Total number of malaria tests conducted at the district level each month using either microscopy or rapid diagnostic test (RDT).
Total number of malaria cases by age and sex	Total number of malaria cases reported at the district level each month stratified by sex and age groups. The age groups used are 0-4 years old, 5-9 years old, 10-14 years old, and over 14 years old.
Total number of malaria cases by parasite species	Total number of malaria cases reported at the district level each month by parasite species. Parasite species recorded are <i>P. falciparum</i> , <i>P. vivax</i> , <i>P. knowlesi</i> , <i>P. malariae</i> and <i>P. ovale</i> . Mixed infections of <i>P. falciparum</i> and <i>P. vivax</i> are recorded as a separate variable.

Table S5.2. Indonesia population by regions, based on the 2020 Census (Badan Pusat Statistik, 2021).

Region	Population in million people (percentage of total)
Sumatra	58.56 (21.67%)
Java and Bali	155.91 (57.70%)
Kalimantan	10.65 (3.94%)
Sulawesi	16.63 (6.15%)
Nusa Tenggara	19.90 (7.36%)
Maluku	3.13 (1.16%)
Papua	5.44 (2.01%)

Table S5.3. National level yearly malaria cases per 1,000 population by age groups.

Year	Malaria cases per 1,000 population (% over all groups)			
	0-4 years old	5-9 years old	10-14 years old	Over 15 years old
2010	3.894 (40%)	2.736 (28%)	2.045 (21%)	1.141 (12%)
2011	3.144 (37%)	2.300 (27%)	1.819 (22%)	1.157 (14%)
2012	4.143 (38%)	3.034 (28%)	2.306 (21%)	1.533 (14%)
2013	3.537 (37%)	2.688 (28%)	2.214 (23%)	1.226 (13%)
2014	2.465 (35%)	2.006 (29%)	1.648 (24%)	0.868 (12%)
2015	1.876 (36%)	1.487 (29%)	1.210 (23%)	0.610 (12%)
2016	1.702 (34%)	1.578 (31%)	1.156 (23%)	0.617 (12%)
2017	2.177 (37%)	1.740 (29%)	1.288 (22%)	0.745 (13%)
2018	1.487 (32%)	1.378 (30%)	1.066 (23%)	0.657 (14%)
2019	1.634 (32%)	1.574 (31%)	1.151 (22%)	0.768 (15%)

Table S5.4. Parameter estimates from GLM: model A.

Model parameters	Mean	SE	SD	Pct 5%	Pct 50%	Pct 95%	n_eff	Rhat
b_1	5.377	0.001	0.037	5.317	5.377	5.438	1435.858	1
b_2	-0.556	0	0.003	-0.561	-0.556	-0.550	1516.219	1.001
b_3	24.643	0.001	0.034	24.587	24.643	24.698	2542.53	1.002
σ	26.436	0.001	0.049	26.356	26.435	26.516	2746.211	1.002

Table S5.5. Parameter estimates from GLM: model B.

Model parameters	Mean	SE	SD	Pct 5%	Pct 50%	Pct 95%	n_eff	Rhat
b_1	16.201	0.011	0.319	15.678	16.193	16.727	798.974	1.005
b_2	-0.163	0	0.004	-0.170	-0.163	-0.156	856.099	1.005
b_3	12.551	0.011	0.312	12.037	12.56	13.066	824.019	1.005
σ	22.536	0.002	0.066	22.427	22.536	22.645	1757.756	1.001

Figures

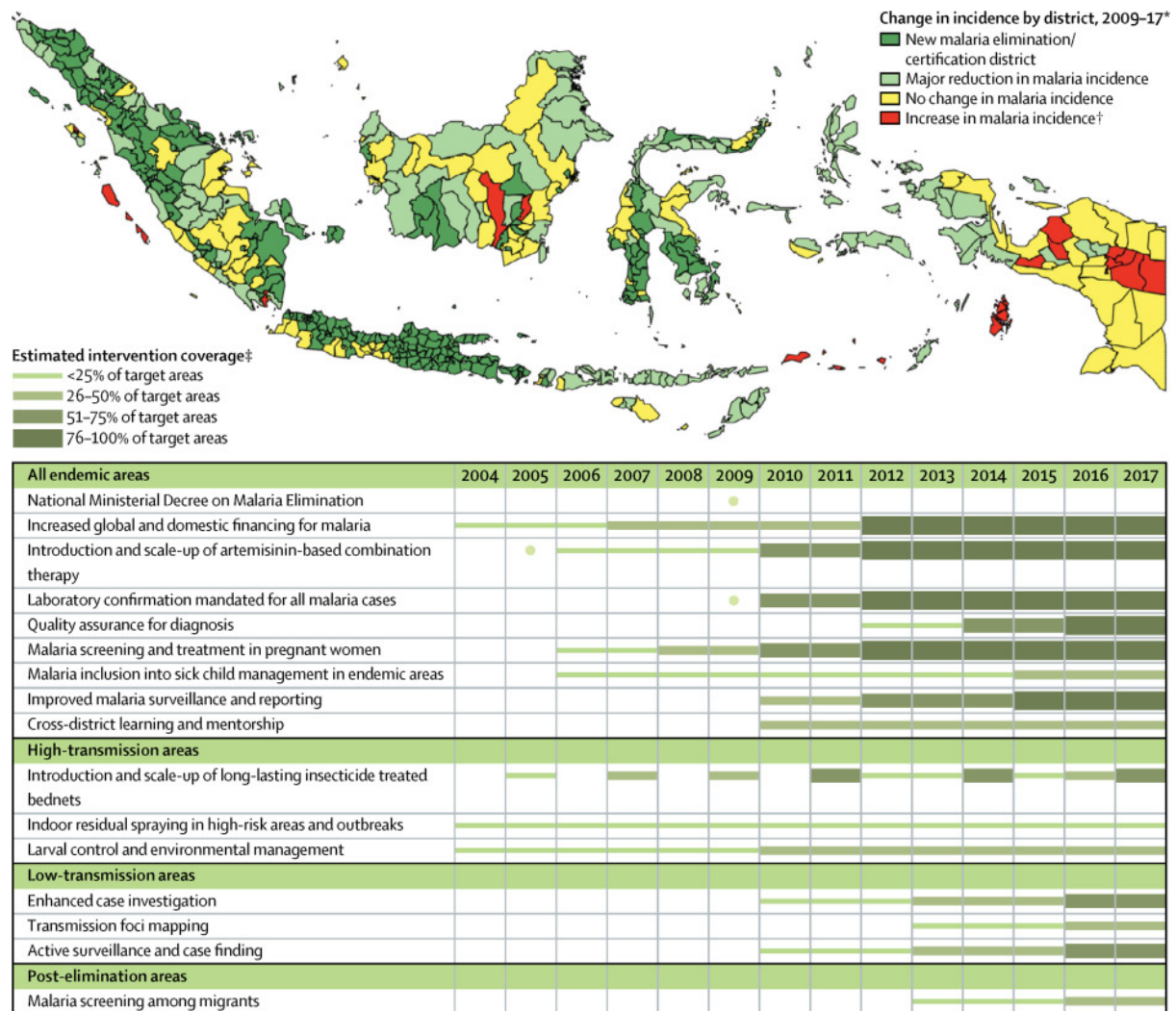


Figure S5.1. Changes in reported malaria incidences and malaria intervention coverages in Indonesia from 2004-2017. The figure is taken from Sitohang et. al. (Sitohang et al., 2018).

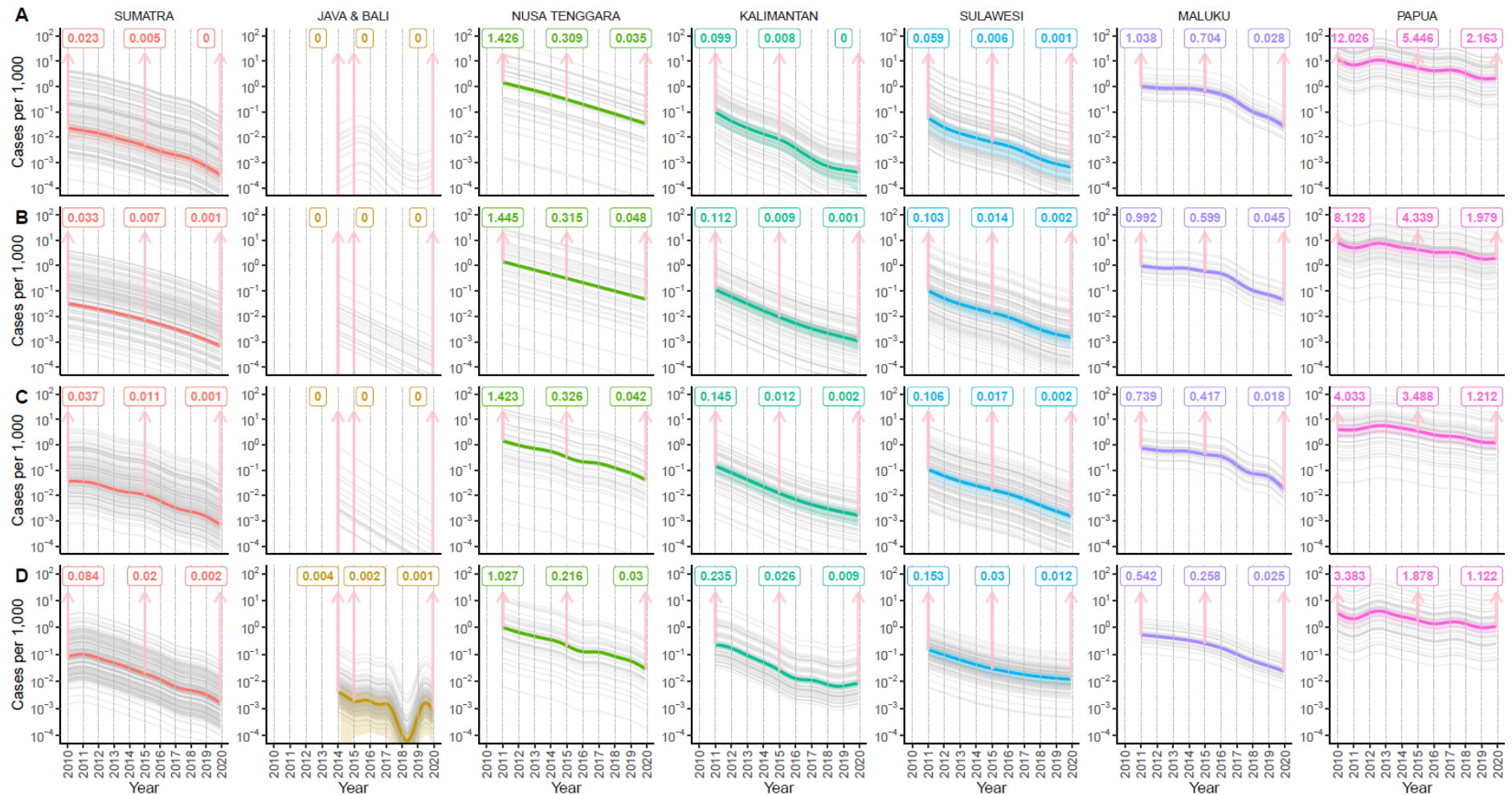


Figure S5.2. Regional-level monthly trends of malaria cases per 1,000 population by age group. The lines denote the median of modelled district-level trends based on Generalised Additive Models. A) 0-4 years old; B) 5-9 years old; C) 10-14 years old; and D) over 15 years old. The numbers denote the median modelled values from GAMs at the beginning of the first year of reported malaria surveillance data from the region, the beginning of 2015, and the end of 2019.

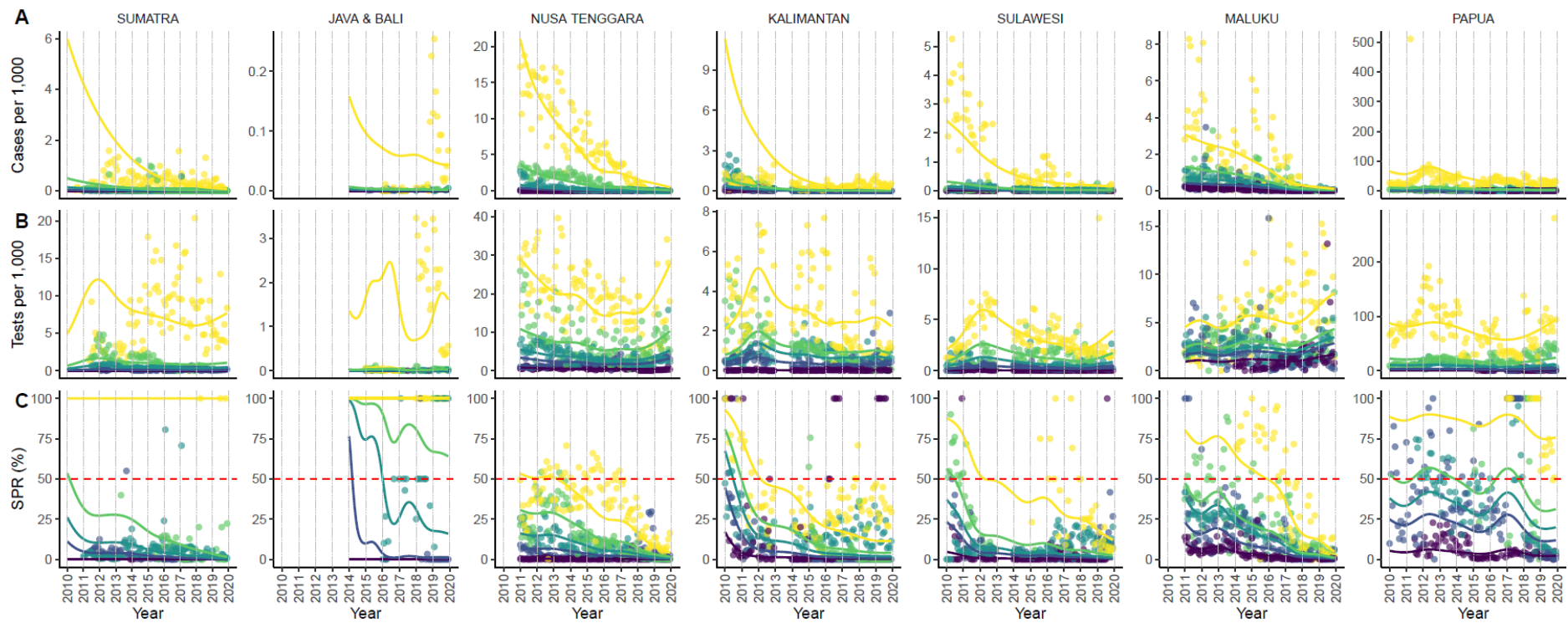


Figure S5.3. District-level Generalised Additive Model fitting examples for A) cases per 1,000 population; B) tests per 1,000 population; and C) test positivity ratio (%). For each region, districts at the 1st (minimum), 2nd, 3rd (median), 4th, and 5th (maximum) quartiles for the estimated intercept at $t = 0$ were selected as examples. Bright colours denote high quartiles, while darker colours denote lower quartiles.

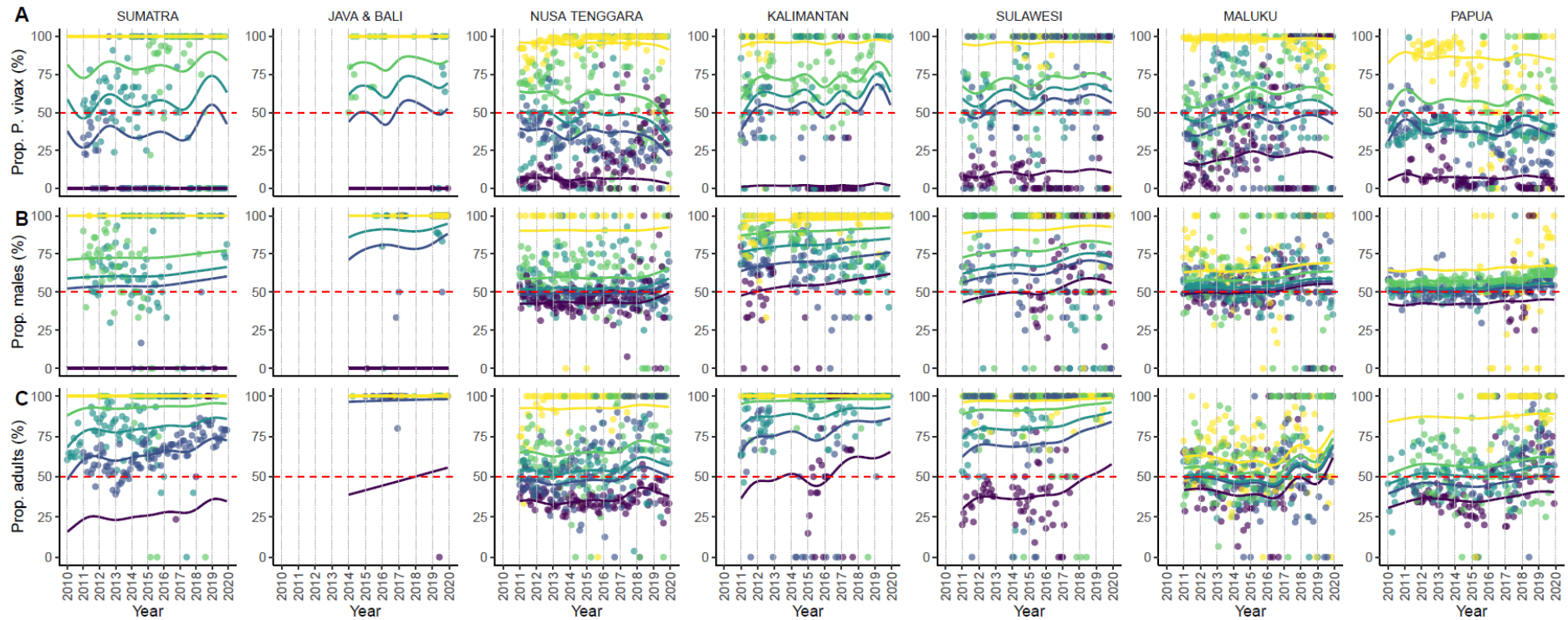


Figure S5.4. District-level Generalised Additive Model fitting examples for A) proportions of *P. vivax* cases; B) proportions of cases in males; and C) proportions of cases in adults (over 15 years old). For each region, districts at the 1st (minimum), 2nd, 3rd (median), 4th, and 5th (maximum) quartiles for the estimated intercept at $t = 0$ were selected as examples. Bright colours denote high quartiles, while darker colours denote lower quartiles.

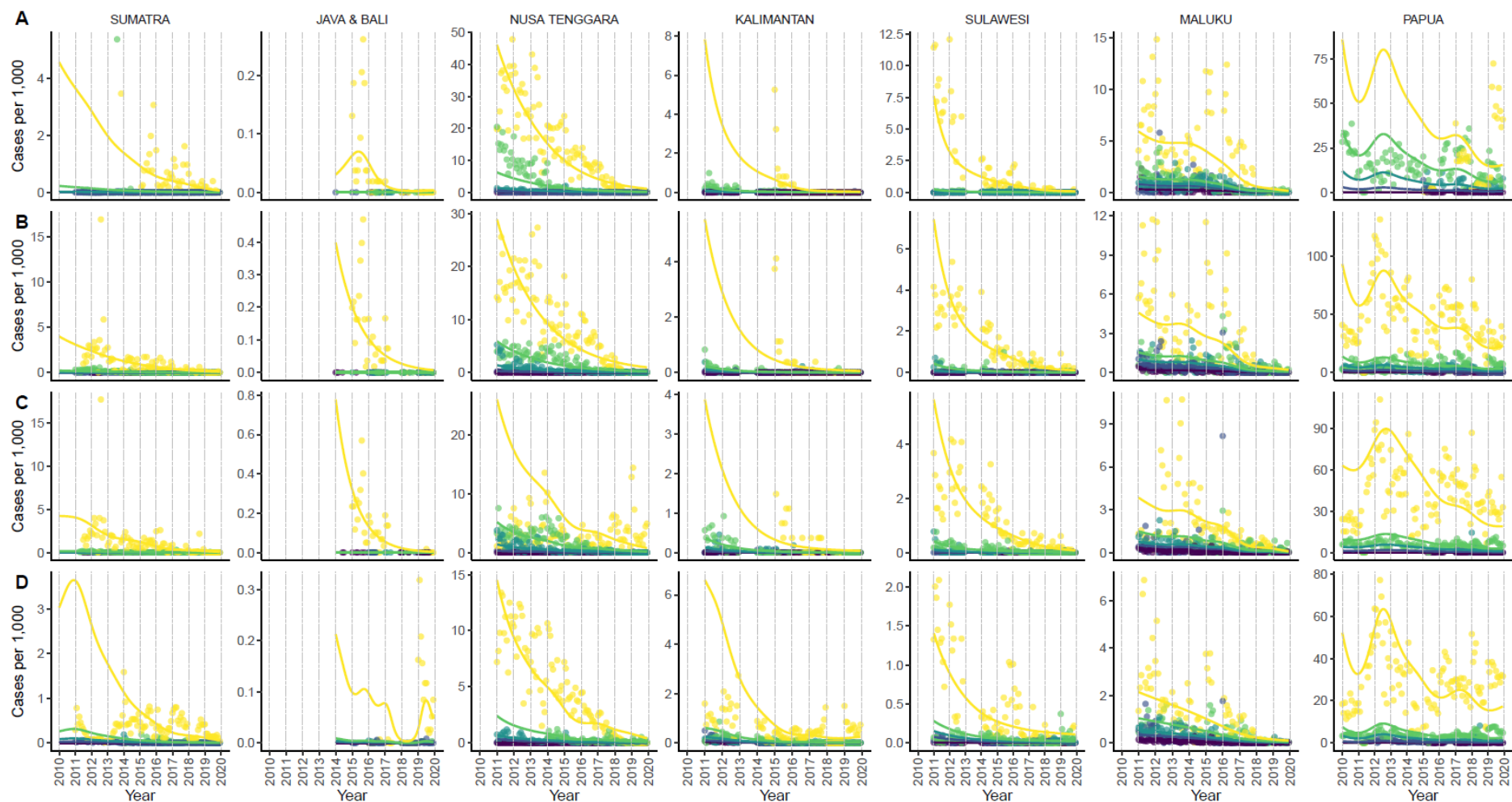


Figure S5.5. District-level GAM fitting examples for A) cases per 1,000 in 0-4 years old age group; B) cases per 1,000 in 5-9 years old age group; C) cases per 1,000 in 10-14 years old age group; and D) cases per 1,000 in over 15 years old age group. For each region, districts at the 1st (minimum), 2nd, 3rd (median), 4th, and 5th (maximum) quartiles for the estimated intercept at $t = 0$ were selected as examples. Bright colours denote high quartiles, while darker colours denote lower quartiles.

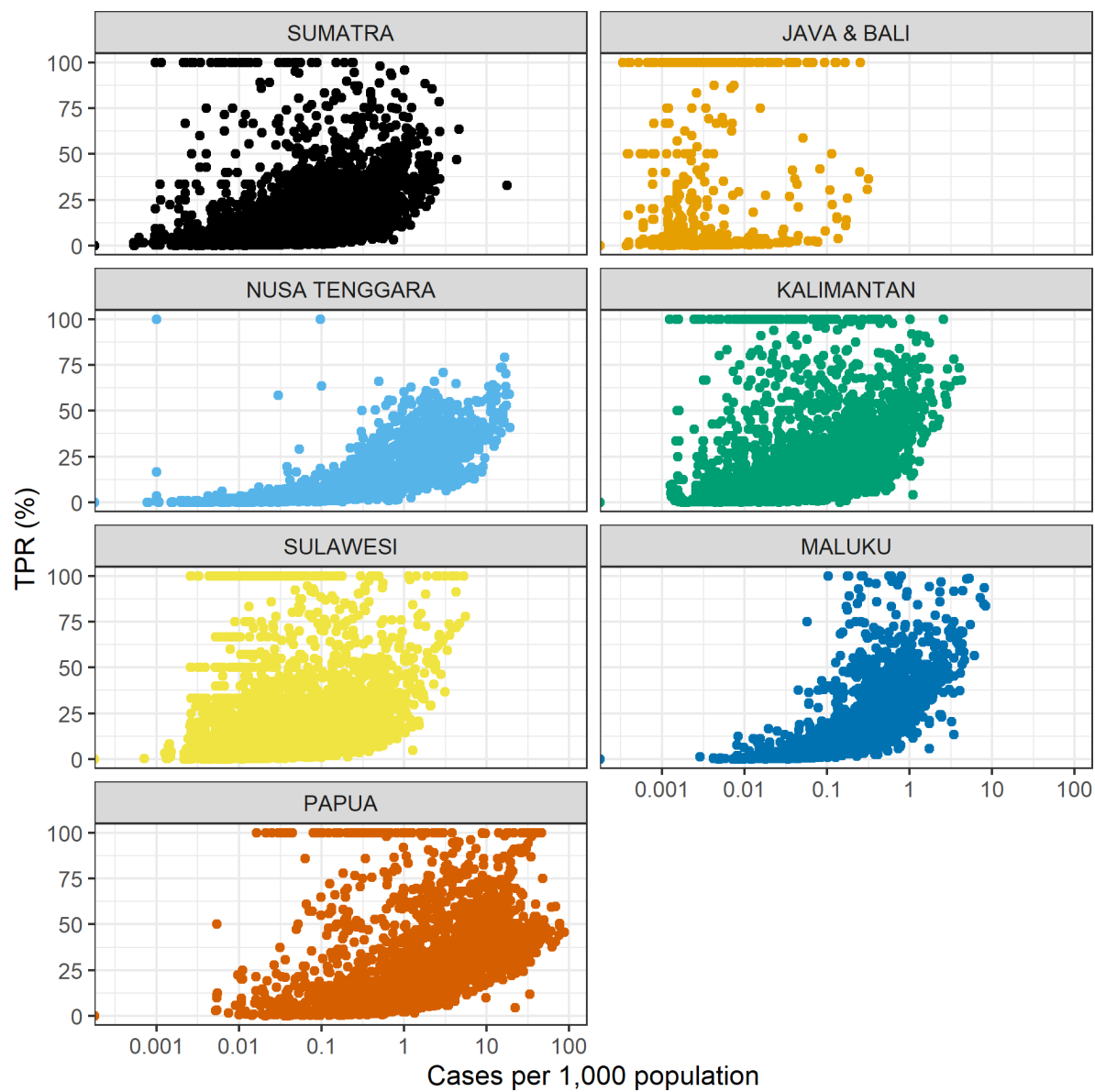


Figure S5.6. Scatter plots of cases per 1,000 population versus test positivity ratio by region based on monthly data.

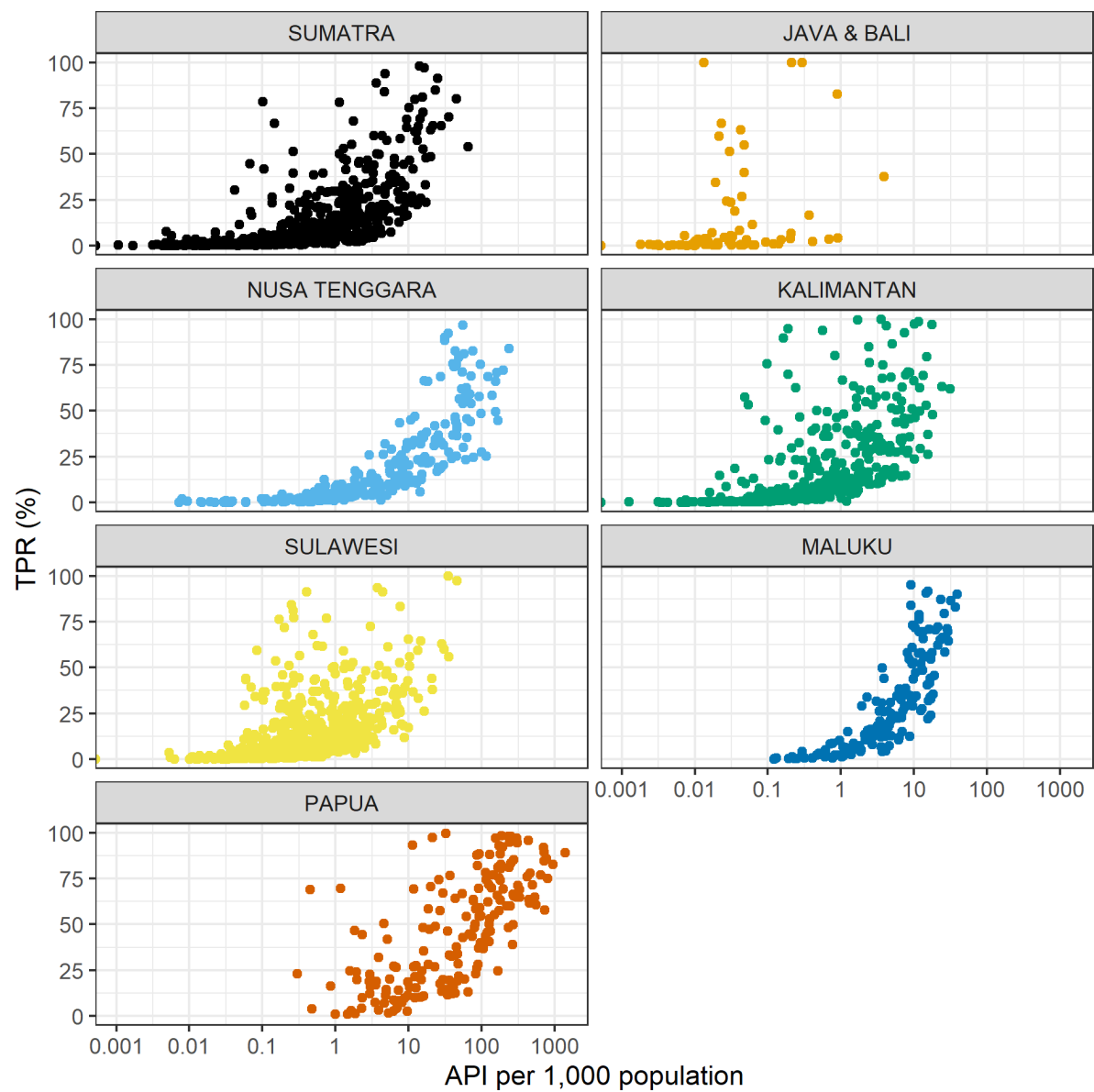


Figure S5.7. Scatter plots of annual parasite incidence (API) per 1,000 population versus test positivity ratio by region based on yearly data.

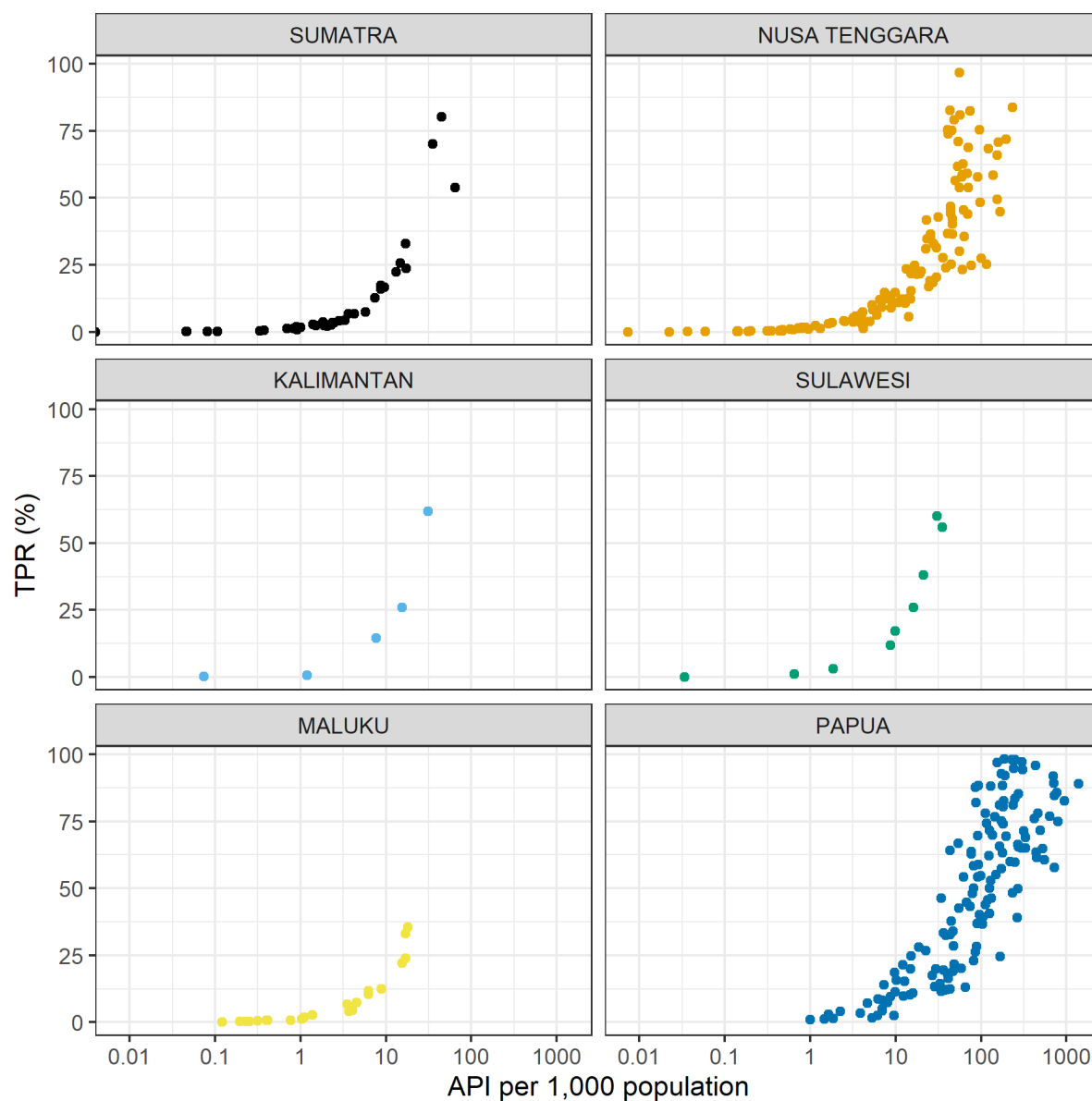


Figure S5.8. Scatter plots of annual parasite incidence (API) per 1,000 population versus test positivity ratio by region based on yearly data but only showing observations with ABER > 5%. Note that no districts in Java and Bali recorder ABER at least 5% over the 2010-2019 decade.

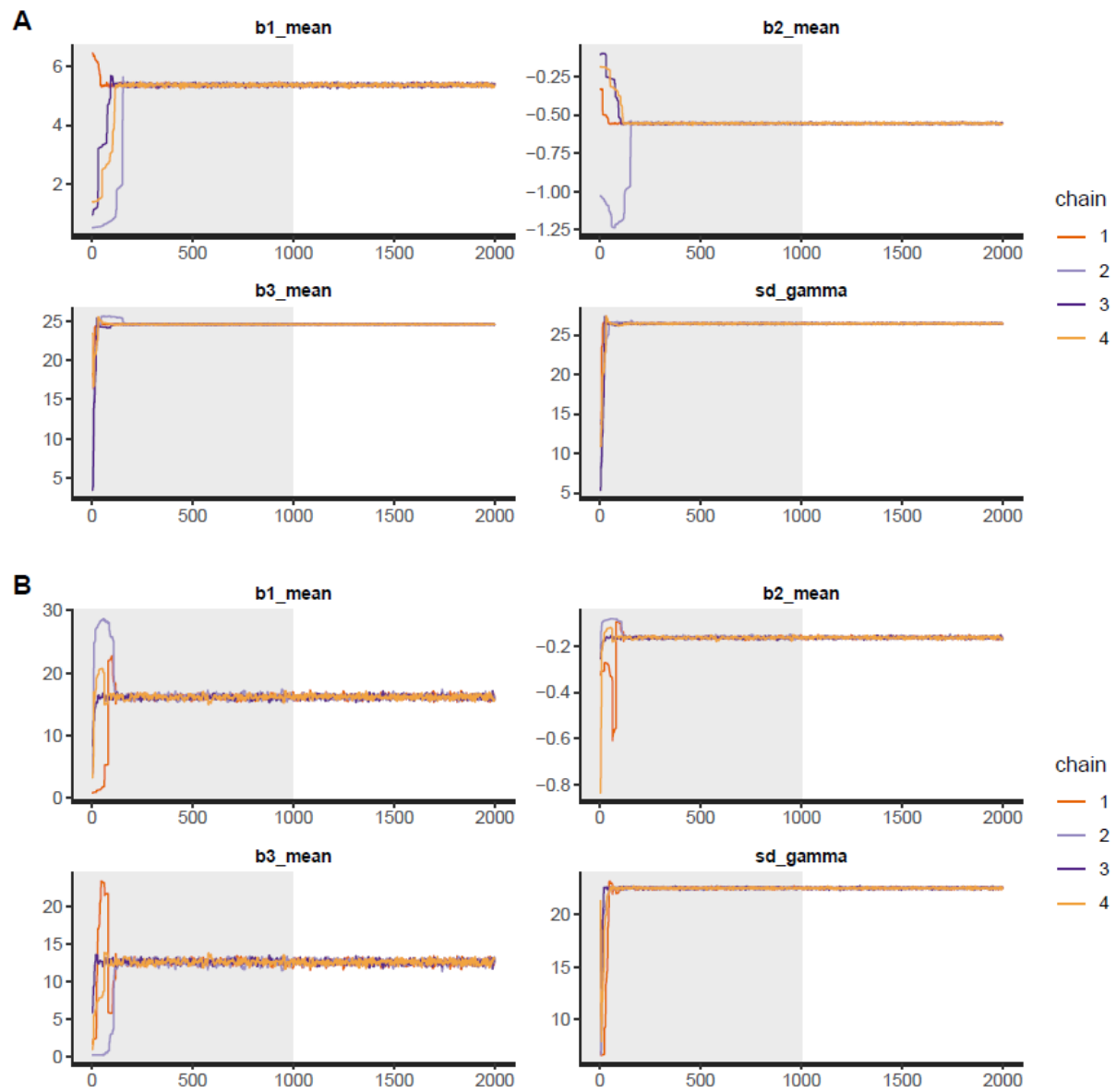


Figure S5.9. Trace plots for GLM fitting in Stan for model A and model B.

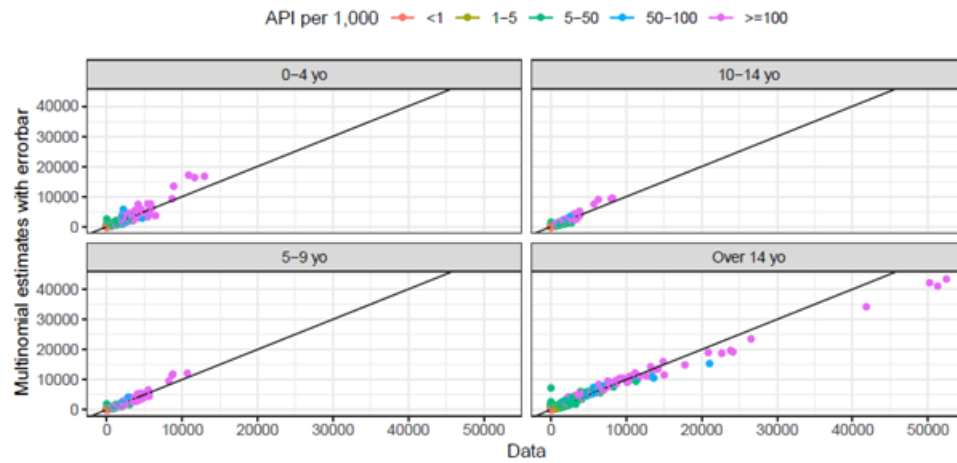


Figure S5.10. Plots of case counts by age groups compared to modelled estimates using GLM. Diagonal lines denote $y = x$.

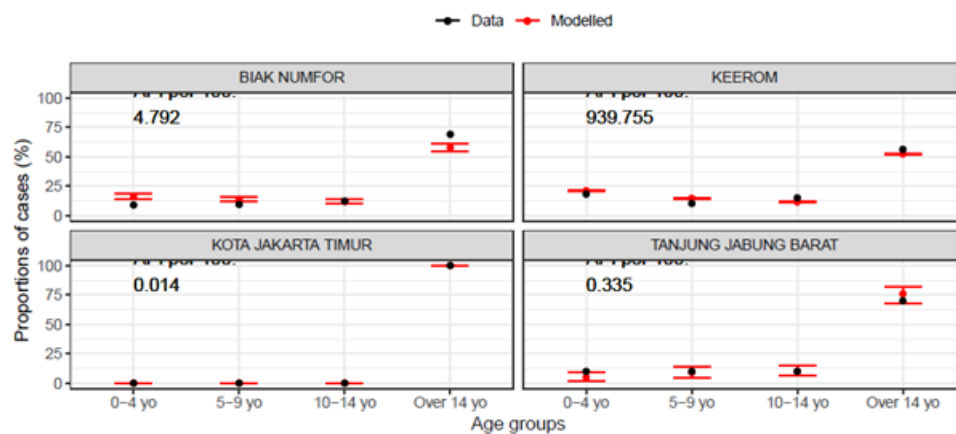


Figure S5.11. Plots of proportions of cases by age groups (black dots) compared to modelled estimates using GLM (red dots with error bars). Data selected were data from districts with minimum, maximum, 25th percentile, and 75th percentile.

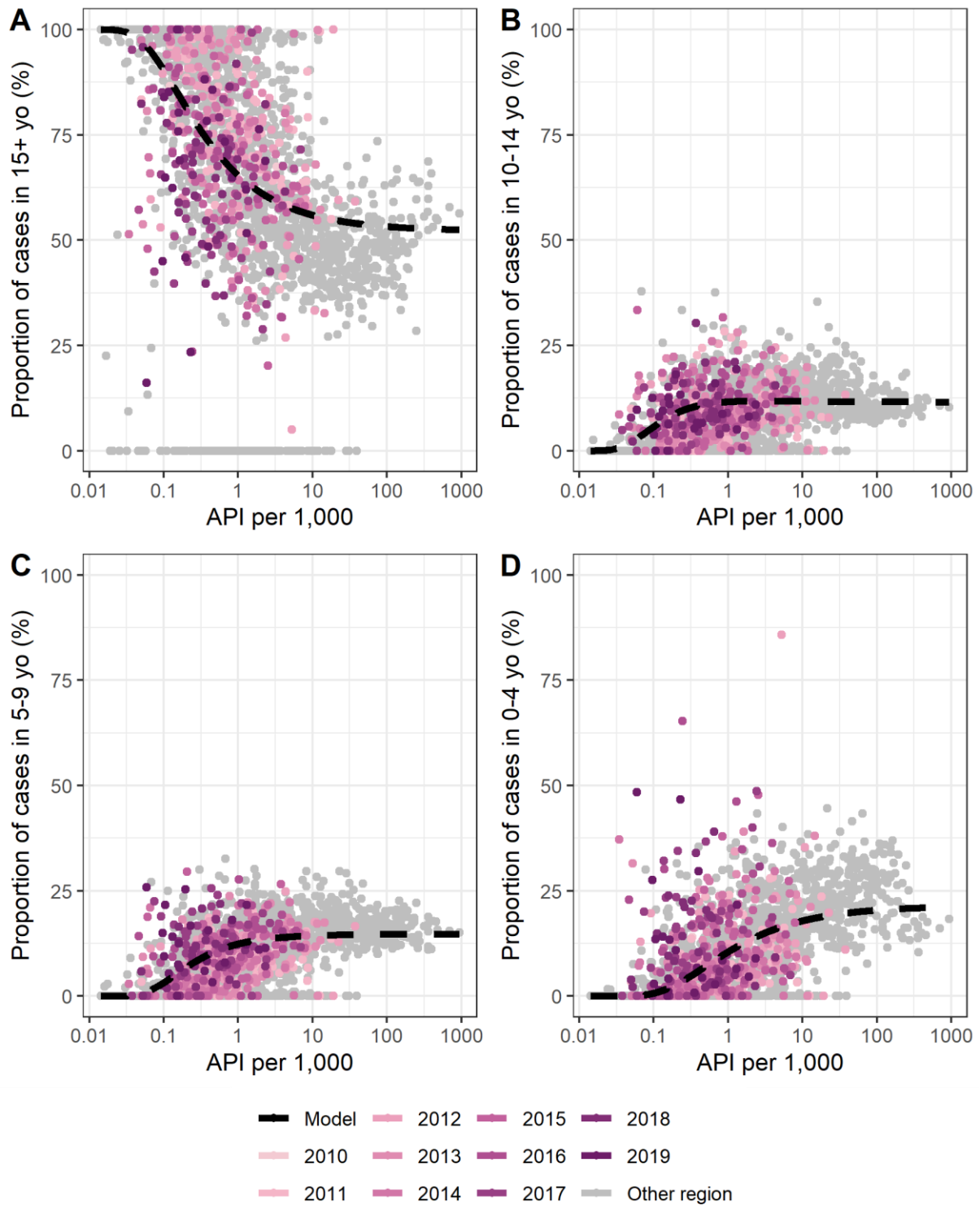


Figure S5.12. Modelled relationships between API per 1,000 and proportion of cases in people aged over 15 (A), 10-14 (B), 5-9 (C), and 0-4 years old (D) with overlaid data from routine surveillance. Dashed lines denote the median of GLM estimates of the relationship. The colours of data points represent years of data collected from Sumatra region.

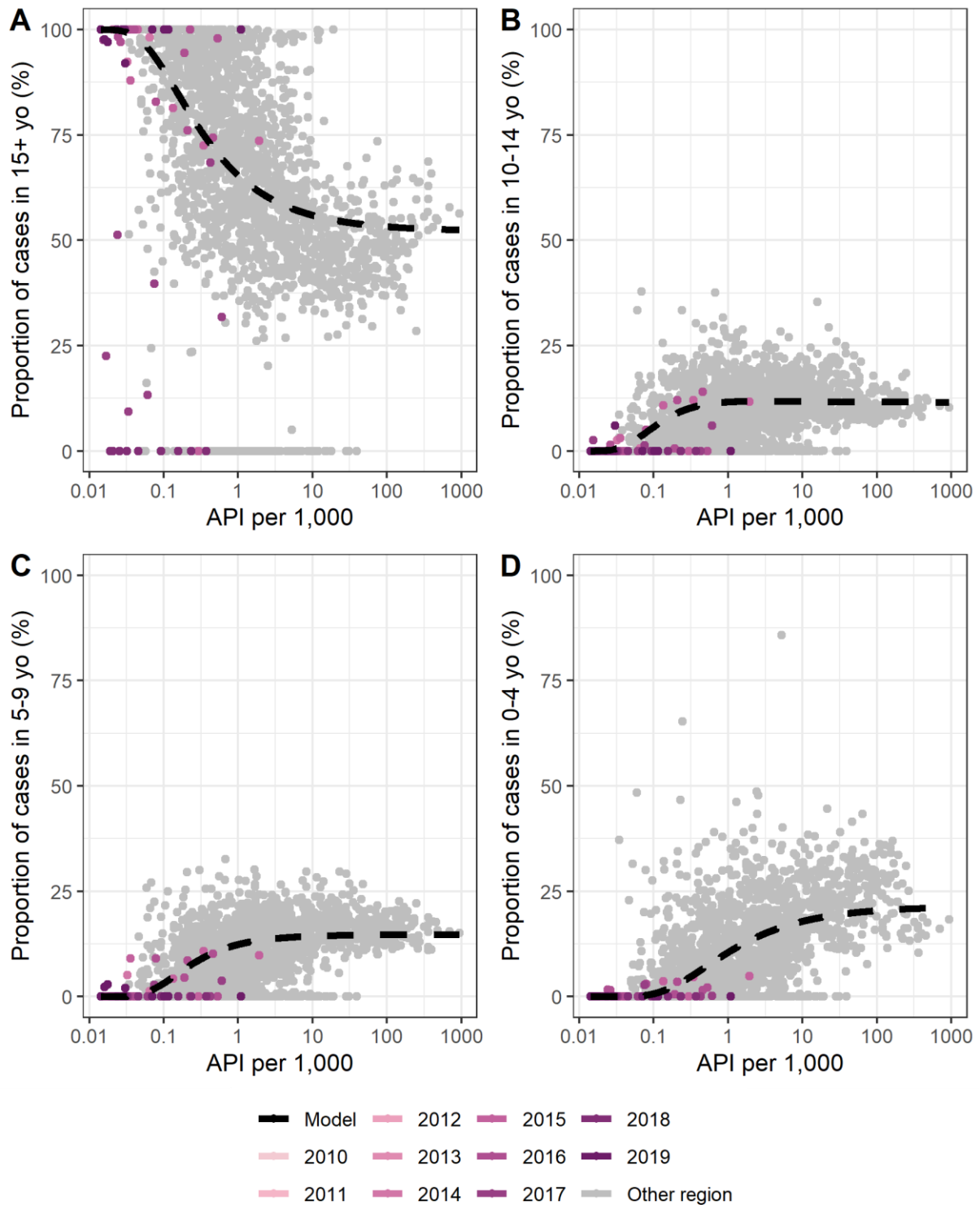


Figure S5.13. Modelled relationships between API per 1,000 and proportion of cases in people aged over 15 (A), 10-14 (B), 5-9 (C), and 0-4 years old (D) with overlaid data from routine surveillance. Dashed lines denote the median of GLM estimates of the relationship. The colours of data points represent years of data collected from Java and Bali region.

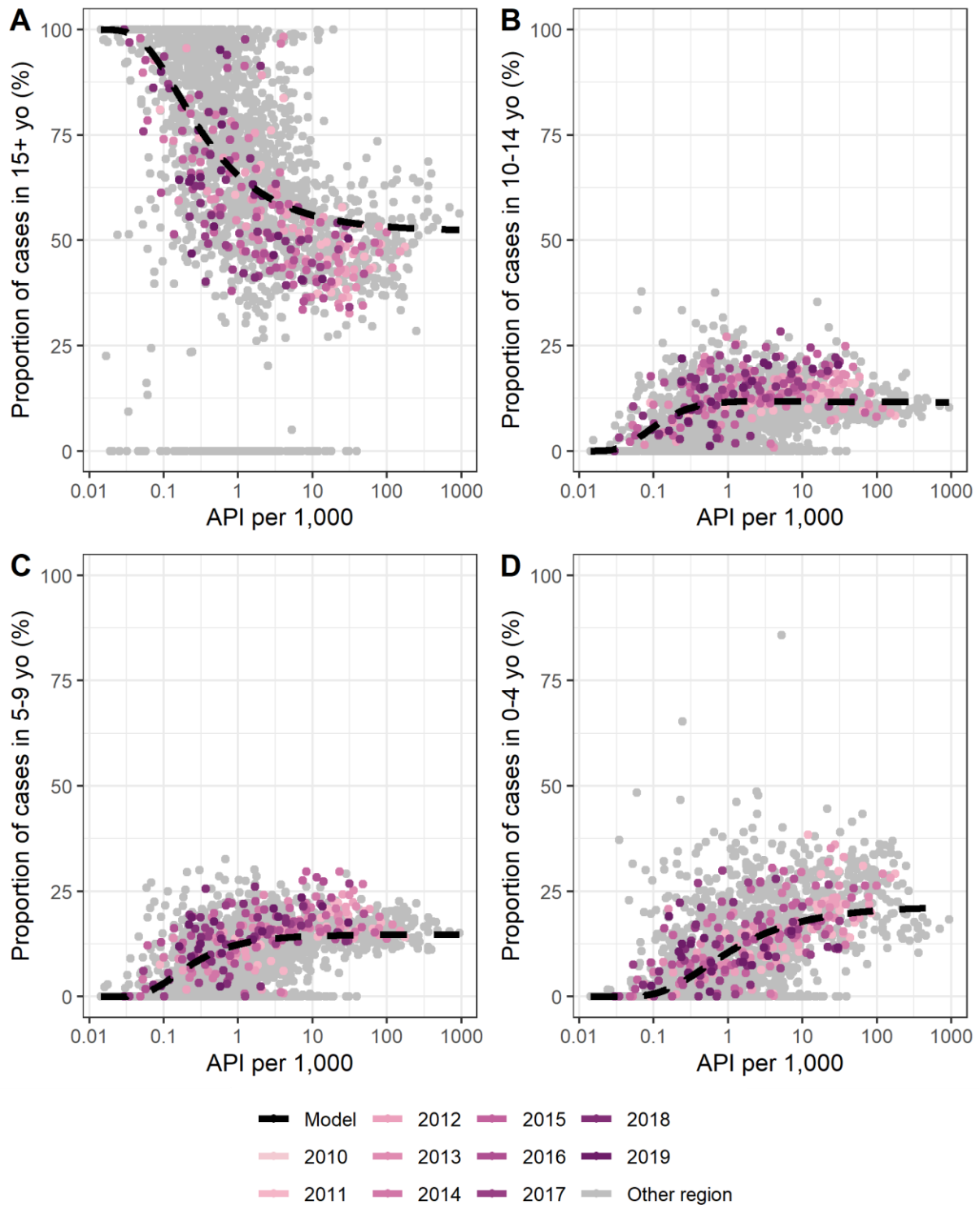


Figure S5.14. Modelled relationships between API per 1,000 and proportion of cases in people aged over 15 (A), 10-14 (B), 5-9 (C), and 0-4 years old (D) with overlaid data from routine surveillance. Dashed lines denote the median of GLM estimates of the relationship. The colours of data points represent years of data collected from Nusa Tenggara region.

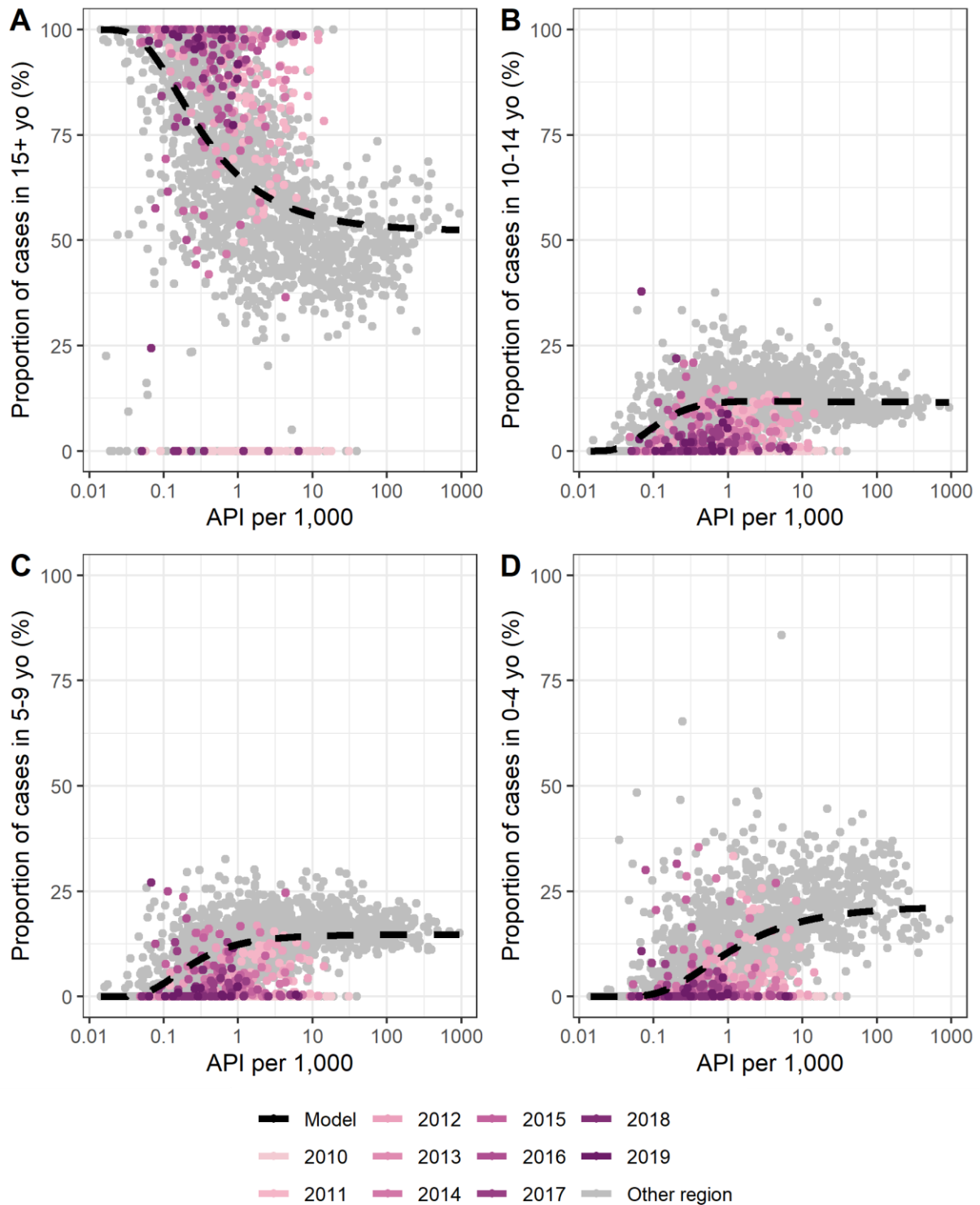


Figure S5.15. Modelled relationships between API per 1,000 and proportion of cases in people aged over 15 (A), 10-14 (B), 5-9 (C), and 0-4 years old (D) with overlaid data from routine surveillance. Dashed lines denote the median of GLM estimates of the relationship. The colours of data points represent years of data collected from Kalimantan region.

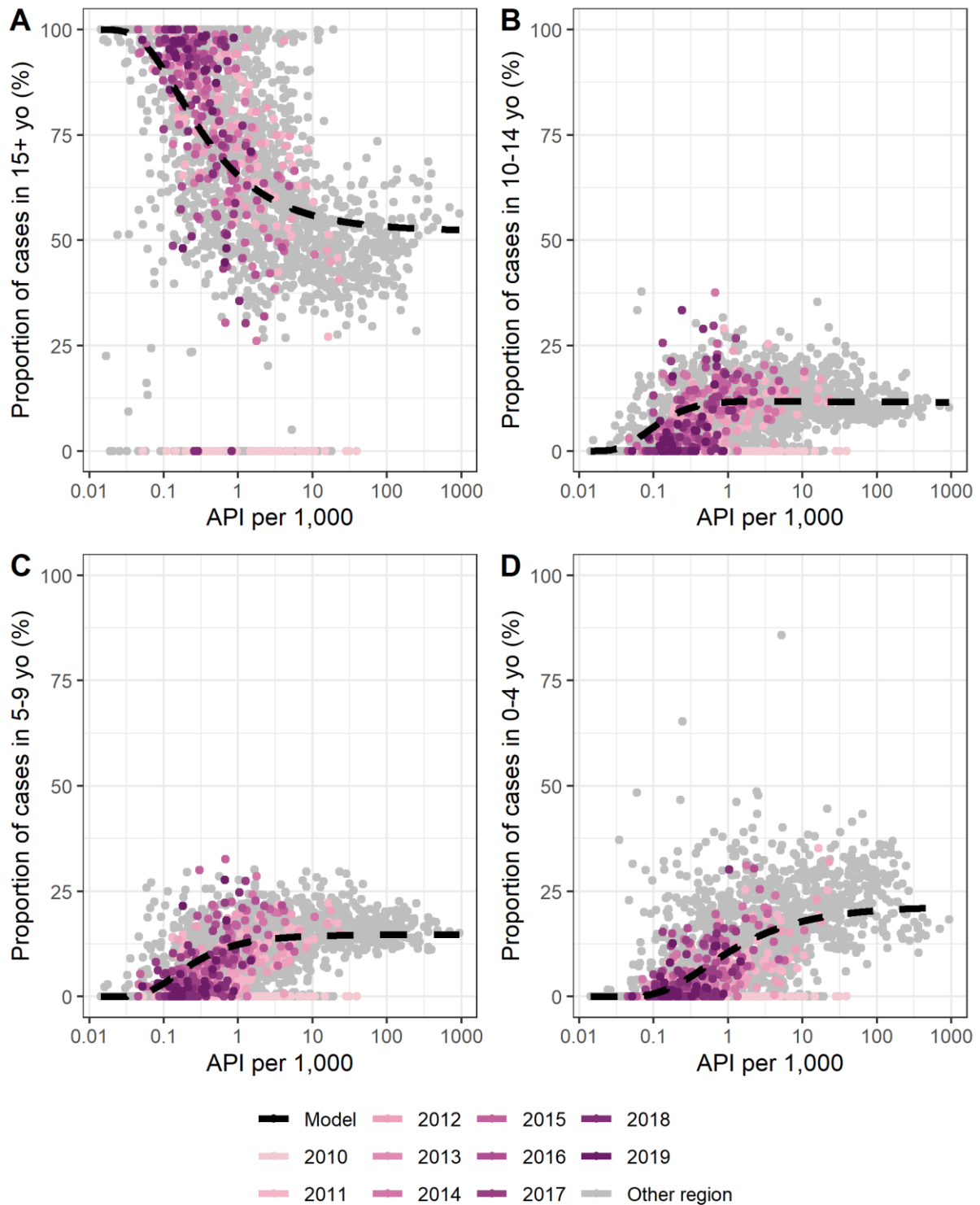


Figure S5.16. Modelled relationships between API per 1,000 and proportion of cases in people aged over 15 (A), 10-14 (B), 5-9 (C), and 0-4 years old (D) with overlaid data from routine surveillance. Dashed lines denote the median of GLM estimates of the relationship. The colours of data points represent years of data collected from Sulawesi region.

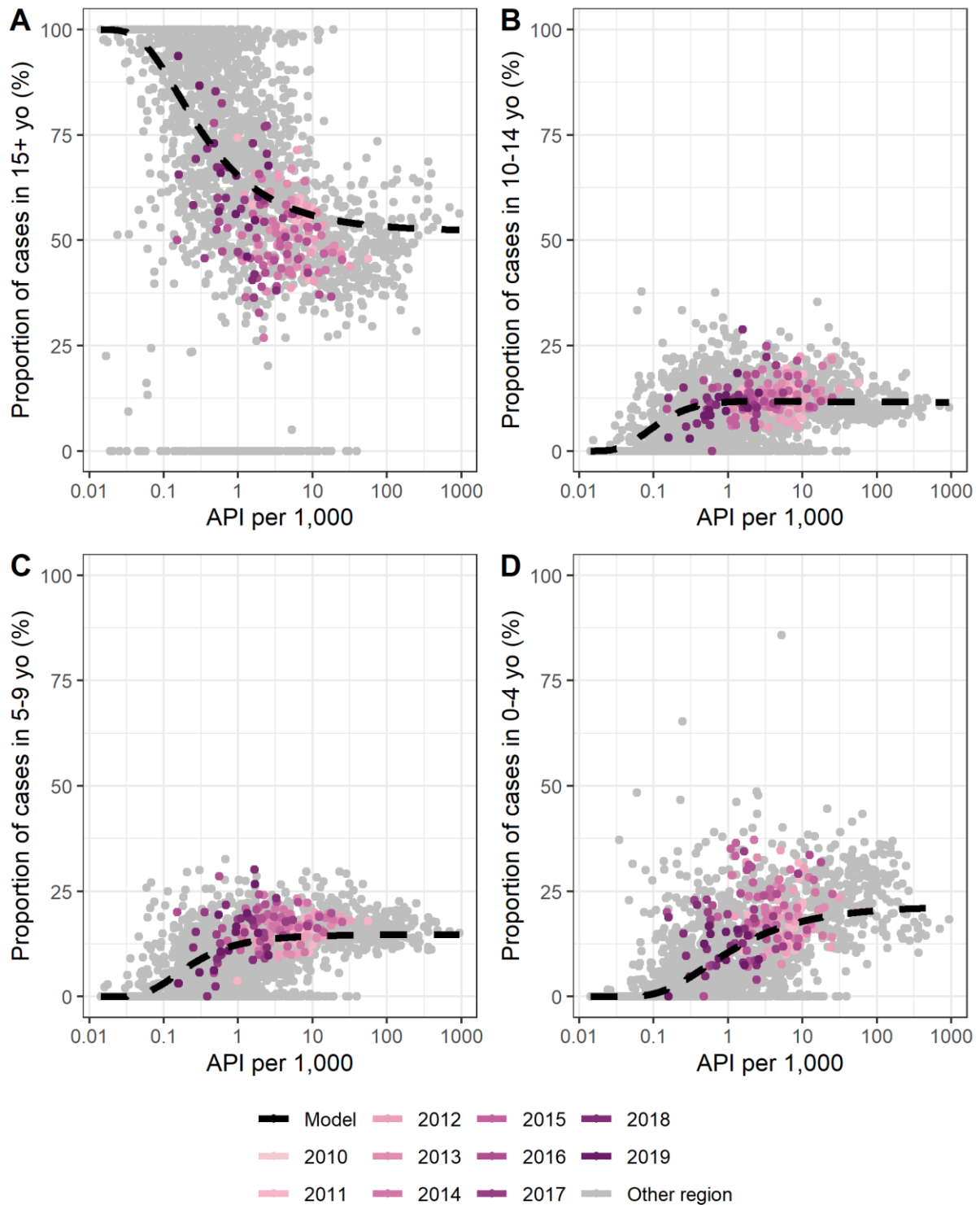


Figure S5.17. Modelled relationships between API per 1,000 and proportion of cases in people aged over 15 (A), 10-14 (B), 5-9 (C), and 0-4 years old (D) with overlaid data from routine surveillance. Dashed lines denote the median of GLM estimates of the relationship. The colours of data points represent years of data collected from Maluku region.

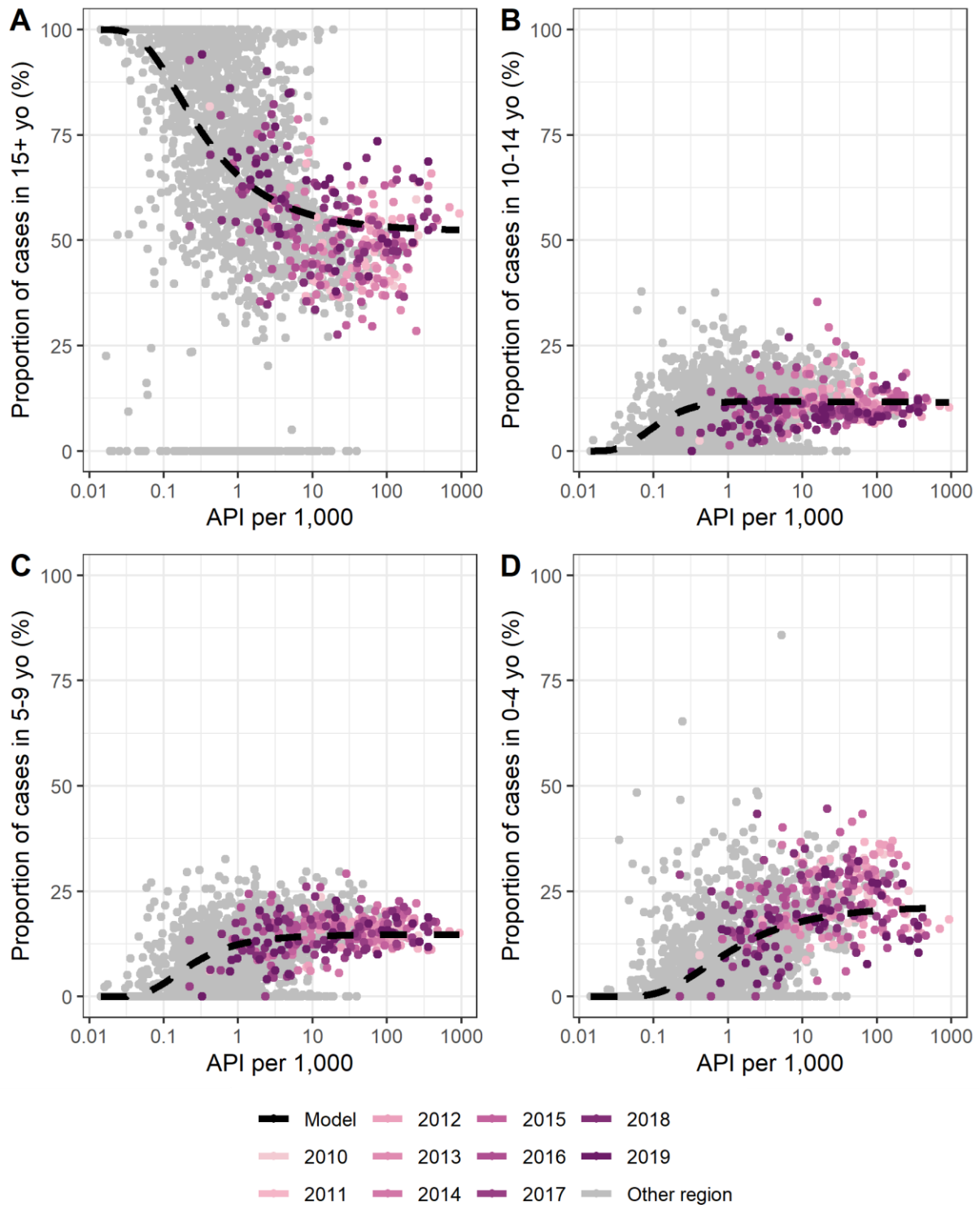


Figure S5.18. Modelled relationships between API per 1,000 and proportion of cases in people aged over 15 (A), 10-14 (B), 5-9 (C), and 0-4 years old (D) with overlaid data from routine surveillance. Dashed lines denote the median of GLM estimates of the relationship. The colours of data points represent years of data collected from Papua region.

Chapter 6 supplementary materials

Methods

Scenario assessment using mathematical model simulations

The mechanistic mathematical model of malaria represents a biological framework of malaria transmission. Simulations generated by these models were used to explain the biological plausibility linking malaria interventions and health outcomes observed, which is one of the Bradford Hill criteria for assessing causality. I used the Imperial College London *Plasmodium falciparum* malaria model (Griffin et al., 2010, 2014) implemented using the `malariasimulation` package (Charles et al., 2022) in R to simulate scenarios of various malaria interventions implemented (i.e., LLIN mass distribution campaigns and scale-up of Artemisinin-based Combination Therapy, ACT, coverage) in a single hypothetical population.

I simulated several simulation scenarios that represent the impacts of gradual scale-up of ACT treatment, a single LLIN mass distribution campaign, multi-year LLIN mass distribution campaigns (**Table S6.2**), and combinations of those interventions on the simulated clinical incidence of *P. falciparum* malaria. I also simulated the baseline scenario where no gradual scale-up of ACT treatment nor LLIN mass distribution campaign was conducted. In addition, the LLIN mass distribution campaigns were simulated to represent campaigns lasting six months to reach the desired coverage within a year (from July to December). This produced a more gradual decline in the simulated incidence over the months rather than a steep decline when a single and large LLIN coverage was simulated. However, the simulations did not consider net top-ups via routine distributions (e.g., ante-natal care distributions) and assumed a loss of efficacy of mosquito nets over time. The complete simulation scenarios and selected mathematical model parameters are shown in **Tables S6.2** and **S6.3**.

Tables

Table S6.1. List of districts conducting LLIN mass distribution campaigns for each group within in each region.

Region	Years conducting mass LLIN campaigns	Districts conducting
Kalimantan	1. 2010	Sambas, Landak, Mempawah, Sanggau, Ketapang, Sintang, Kapuas Hulu, Melawi, Kayong Utara, Kota Singkawang, Kotawaringin Barat, Barito Selatan, Barito Utara, Sukamara, Lamandau, Katingan, Murung Raya, Kota Baru, Tabalong, Penajam Paser Utara

	2. 2011	Malinau
Sulawesi	1. 2011	Bolaang Mongondow, Kepulauan Sangihe, Kepulauan Talaud, Minahasa Selatan, Minahasa Utara, Bolaang Mongondow Utara, Minahasa Tenggara, Kota Bitung, Kota Kotamobagu, Banggai, Morowali, Poso, Donggala, Toli-toli, Buol, Parigi Moutong, Tojo Una-una, Kepulauan Selayar, Konawe, Bombana, Buton Utara, Kota Bau, Pohuwato, Gorontalo Utara, Kota Gorontalo, Mamuju, Mamuju Utara
	2. 2011 & 2014	Banggai Kepulauan, Buton
Sumatra	1. 2014	Aceh Jaya
Nusa Tenggara	1. 2014	Belu, Flores Timur, Rote Ndao, Manggarai Barat
	2. 2014 & 2017	Sumba Barat, Sumba Timur, Alor, Lembata, Sikka, Ende, Sumba Tengah, Sumba Barat Daya, Nagekeo, Sabu Raijua, Malaka
	3. 2016	Kupang, Timor Tengah Selatan, Timor Tengah Utara, Ngada, Manggarai, Manggarai Timur, Kota Kupang
Maluku	1. 2014 & 2016	Maluku Tenggara
	2. 2014 & 2017	Kepulauan Aru, Seram Bagian Barat, Seram Bagian Timur, Maluku Barat Daya, Buru Selatan, Kepulauan Sula, Halmahera Utara, Halmahera Timur, Pulau Morotai, Pulau Taliabu
	3. 2016	Maluku Tenggara Barat, Buru, Halmahera Tengah, Halmahera Selatan, Kota Ternate
Papua	1. 2014 & 2017	Kaimana, Teluk Wondama, Teluk Bintuni, Manokwari, Sorong Selatan, Sorong, Raja Ampat, Tambrauw, Maybrat, Kota Sorong, Merauke, Jayapura, Nabire, Kepulauan Yapen, Biak Numfor, Mimika, Boven Digoel, Mappi, Asmat, Sarmi, Keerom, Supiori, Mamberamo Raya, Kota Jayapura
	2. 2017	Fakfak, Manokwari Selatan, Pegunungan Arfak, Puncak Jaya, Pegunungan Bintang, Mamberamo Tengah, Yalimo

Table S6.2. Simulation scenarios of mathematical models of malaria.

Scenario	Scale-up of ACT in 2010 (70% coverage)	Mass LLIN campaign in 2010 (80% coverage)	Mass LLIN campaign in 2013 (50% coverage)	Mass LLIN campaign in 2013 (80% coverage)	Mass LLIN campaign in 2014 (80% coverage)
Baseline	-	-	-	-	-
ACT 2010	v	-	-	-	-
Mass LLIN campaign 2010	-	v	-	-	-
Mass LLIN campaign 2014	-	-	-	-	v
Mass LLIN campaigns 2010 & 2013 (80% & 50%)	-	v	v	-	-
Mass LLIN campaigns 2010 & 2013 (80% & 80%)	-	v	-	v	-

Table S6.3. Selected malaria model parameters and their descriptions.

Parameter	Value	Descriptions
ACT ₁	30%	First introduction of ACT as malaria treatment in 2004 with 30% coverage
ACT ₂	70%	Scale-up of ACT as malaria treatment in 2010 to 70% coverage
LLIN ₁	80%	Mass LLIN campaign in 2010 with 80% coverage
LLIN ₂	80%	2 nd mass LLIN campaign in 2013 with 50% coverage
LLIN ₃	80%	2 nd mass LLIN campaign in 2013 with 60% coverage
LLIN ₄	50%	Mass LLIN campaign in 2014 with 80% coverage
EIR	2	Baseline entomological inoculation rate (EIR) for model simulation

Chapter 7 supplementary materials

Methods

Imputing 2010-2017 district-level reporting completeness

For the imputations of the district-level reporting completeness from 2010 to 2017, there are two steps:

- 1) First, reasonable imputations based on the ratio of reported malaria tests were done to impute missing data on province-level reporting completeness (R_{prov}) (**Figure S7.2**). For years with missing data, the imputed values were calculated using the ratio between the number of tests conducted in that year and the number of tests conducted in the nearest year where reporting completeness data is available and then multiplied by the reporting completeness from the denominator year.
- 2) Then, imputations of district-level reporting completeness for years before 2018 were done, accounting for province-level reporting completeness, the number of primary health centres within each district, and average district contribution to the overall province-level reporting in 2018 and 2019.
 - a. The district contribution was the proportion of total primary health centre routine surveillance data reports within a district over the year (total primary health centres (NP_i) $\times$ 12 months, T_i , with i as the index of a district within a province) to the province-level total primary health centre reports that year (T_{prov} , which maximum value is $\sum_{i=1}^d T_i$).
 - b. The average district contribution value of 2018 and 2019 was assumed to be each year's average contribution across 2010-2017 (A_i).
 - c. Then for each year, the weighted province-level contribution for each district was calculated by removing the contributions from districts that were not reporting their routine data that year ($B_i = \frac{A_i \times Z_i}{\sum_{i=1}^d A_i \times Z_i}$, with Z_i as the reporting index of the district in that year, 0 means no report and 1 means there was report, and d is the total number of districts in a province).
 - d. The province-level total primary health centre reports over the year were then calculated by multiplying reporting completeness and the total possible over-the-year reports from primary health centres ($C_{prov} = R_{prov} \times T_{prov}$).

- e. Each district's estimated primary health centre reports over the year were calculated by multiplying the district's weighted contribution by the province-level estimated total reports ($D_i = B_i \times C_{prov}$).
- f. Finally, district-level reporting completeness was calculated by calculating the proportion of the estimated district-level primary health centre reports over the year to the total possible district-level primary health centre reports over the year ($R_i = \frac{D_i}{T_i}$).

The district-level reporting completeness, including the imputed data for 2010-2017 (R_i for each year), is shown in **Figure S7.3**.

Tables

Table S7.1. List of districts in Papua region as references for district-level map in **Figure S1**.

No	Province	District
1	Papua Barat	Fakfak
2	Papua Barat	Kaimana
3	Papua Barat	Teluk Wondama
4	Papua Barat	Teluk Bintuni
5	Papua Barat	Manokwari
6	Papua Barat	Sorong Selatan
7	Papua Barat	Sorong
8	Papua Barat	Raja Ampat
9	Papua Barat	Tambrau
10	Papua Barat	Maybrat
11	Papua Barat	Manokwari Selatan
12	Papua Barat	Pegunungan Arfak
13	Papua Barat	Kota Sorong
14	Papua	Merauke
15	Papua	Jayawijaya
16	Papua	Jayapura
17	Papua	Nabire
18	Papua	Kepulauan Yapen
19	Papua	Biak Numfor
20	Papua	Paniai
21	Papua	Puncak Jaya
22	Papua	Mimika
23	Papua	Boven Digoel
24	Papua	Mappi
25	Papua	Asmat

26	Papua	Yahukimo
27	Papua	Pegunungan Bintang
28	Papua	Tolikara
29	Papua	Sarmi
30	Papua	Keerom
31	Papua	Waropen
32	Papua	Supiori
33	Papua	Mamberamo Raya
34	Papua	Nduga
35	Papua	Lanny Jaya
36	Papua	Mamberamo Tengah
37	Papua	Yalimo
38	Papua	Puncak
39	Papua	Dogiyai
40	Papua	Intan Jaya
41	Papua	Deiyai
42	Papua	Kota Jayapura

Table S7.2. Values and sources of treatment-seeking behaviour data.

Province	Year	Parameters	Value	Notes	Sources
Papua Barat	2012	Seeking treatment in the public sector when having fever in the last 2 weeks	48.4%	Province-level estimate from DHS survey	(Statistics Indonesia - Badan Pusat Statistik - BPS et al., 2013)
Papua Barat	2012	Seeking treatment in the private sector when having fever in the last 2 weeks	20.0%	Province-level estimate from DHS survey	(Statistics Indonesia - Badan Pusat Statistik - BPS et al., 2013)
Papua Barat	2017	Seeking treatment in the public sector when having fever in the last 2 weeks	72.2%	Province-level estimate from DHS survey	(National Population and Family Planning Board et al., 2018)
Papua Barat	2017	Seeking treatment in the private sector when having fever in the last 2 weeks	10.0%	Province-level estimate from DHS survey	(National Population and Family Planning Board et al., 2018)

Papua	2012	Seeking treatment in the public sector when having fever in the last 2 weeks	65.0%	Province-level estimate from DHS survey	(Statistics Indonesia - Badan Pusat Statistik - BPS et al., 2013)
Papua	2012	Seeking treatment in the private sector when having fever in the last 2 weeks	4.8%	Province-level estimate from DHS survey	(Statistics Indonesia - Badan Pusat Statistik - BPS et al., 2013)
Papua	2017	Seeking treatment in the public sector when having fever in the last 2 weeks	44.6%	Province-level estimate from DHS survey	(National Population and Family Planning Board et al., 2018)
Papua	2017	Seeking treatment in the private sector when having fever in the last 2 weeks	20.5%	Province-level estimate from DHS survey	(National Population and Family Planning Board et al., 2018)
Papua	2005	Treatment seeking to public health facilities of malaria patients	45.7%	Study site Mimika, Papua	(Karyana et al., 2016)
Papua	2013	Treatment seeking to public health facilities of malaria patients	67.3%	Study site Mimika, Papua	(Kenangalem et al., 2019)

Table S7.3. Consensus province-level treatment-seeking values for 2005, 2012, and 2017 based on previous surveys and studies.

Province	Year	Assumed treatment-seeking value
Papua Barat	2005	45%
Papua Barat	2012	50%
Papua Barat	2017	70%
Papua	2005	45%
Papua	2012	65%
Papua	2017	45%

Table S7.4. Adult mosquito bionomics for the three dominant malaria mosquito vector species in Papua.

Parameters	Mosquito species			References
	<i>An. punctulatus</i>	<i>An. koliensis</i>	<i>An. farauti</i>	
Human blood index	0.775	0.73	0.5	(White et al., 2018)
Indoor biting proportion	0.871	0.741	0.346	(Fauziah et al., 2012; Kawulur et al., 2014 [†] ; Mofu, 2013; Oktavian, 2014; Saputro et al., 2010; St. Laurent et al., 2016 [†])
	0.88	0.54	0.407	
(average)	0.876	0.641	0.377	
Bedtime biting proportion	0.762	0.864	0.746	
	0.987	0.605	0.368	
(average)	0.874	0.735	0.557	
Life expectancy in days	6	6	6	(White et al., 2018)
Duration of sporogony in days	8.4	8.4	8.4	(Gething et al., 2011; White et al., 2018)
Time spent foraging in days	0.68	0.68	0.68	(Killeen & Smith, 2007; White et al., 2018)
Duration of gonothropic cycle in days	3	3	3	(Clements & Paterson, 1981; White et al., 2018)

[†] Estimates for *An. farauti* 4.

[‡] Estimates for *An. farauti* s.s.

Table S7.5. District-level estimated proportions of the three dominant malaria mosquito vector species in Papua.

Province	District	<i>An. punctulatus</i>	<i>An. farauti</i>	<i>An. koliensis</i>
Papua Barat	Fakfak	0.311	0.356	0.333
Papua Barat	Kaimana	0.328	0.339	0.333
Papua Barat	Teluk Wondama	0.327	0.337	0.336
Papua Barat	Teluk Bintuni	0.300	0.328	0.373
Papua Barat	Manokwari	0.338	0.317	0.345
Papua Barat	Sorong Selatan	0.279	0.320	0.400
Papua Barat	Sorong	0.250	0.370	0.380

Papua Barat	Raja Ampat	0.437	0.506	0.058
Papua Barat	Tambrau	0.300	0.330	0.370
Papua Barat	Maybrat	0.267	0.343	0.390
Papua Barat	Manokwari Selatan	0.404	0.321	0.275
Papua Barat	Pegunungan Arfak	0.378	0.247	0.375
Papua Barat	Kota Sorong	0.216	0.460	0.323
Papua	Merauke	0.279	0.402	0.319
Papua	Jayawijaya	0.337	0.326	0.337
Papua	Jayapura	0.322	0.334	0.343
Papua	Nabire	0.302	0.355	0.343
Papua	Kepulauan Yapen	0.296	0.362	0.342
Papua	Biak Numfor	0.296	0.361	0.343
Papua	Paniai	0.331	0.327	0.342
Papua	Puncak Jaya	0.335	0.338	0.326
Papua	Mimika	0.341	0.315	0.344
Papua	Boven Digoel	0.329	0.339	0.332
Papua	Mappi	0.319	0.342	0.339
Papua	Asmat	0.336	0.341	0.323
Papua	Yahukimo	0.344	0.329	0.327
Papua	Pegunungan Bintang	0.340	0.337	0.323
Papua	Tolikara	0.339	0.331	0.331
Papua	Sarmi	0.324	0.339	0.337
Papua	Keerom	0.315	0.332	0.352
Papua	Waropen	0.316	0.361	0.323
Papua	Supiori	0.353	0.338	0.309
Papua	Mamberamo Raya	0.325	0.340	0.334
Papua	Nduga	0.335	0.339	0.326
Papua	Lanny Jaya	0.335	0.332	0.333
Papua	Mamberamo Tengah	0.332	0.335	0.333
Papua	Yalimo	0.340	0.326	0.334
Papua	Puncak	0.333	0.339	0.328
Papua	Dogiyai	0.350	0.309	0.341
Papua	Intan Jaya	0.330	0.342	0.328
Papua	Deiyai	0.333	0.324	0.344
Papua	Kota Jayapura	0.329	0.335	0.336

Figures

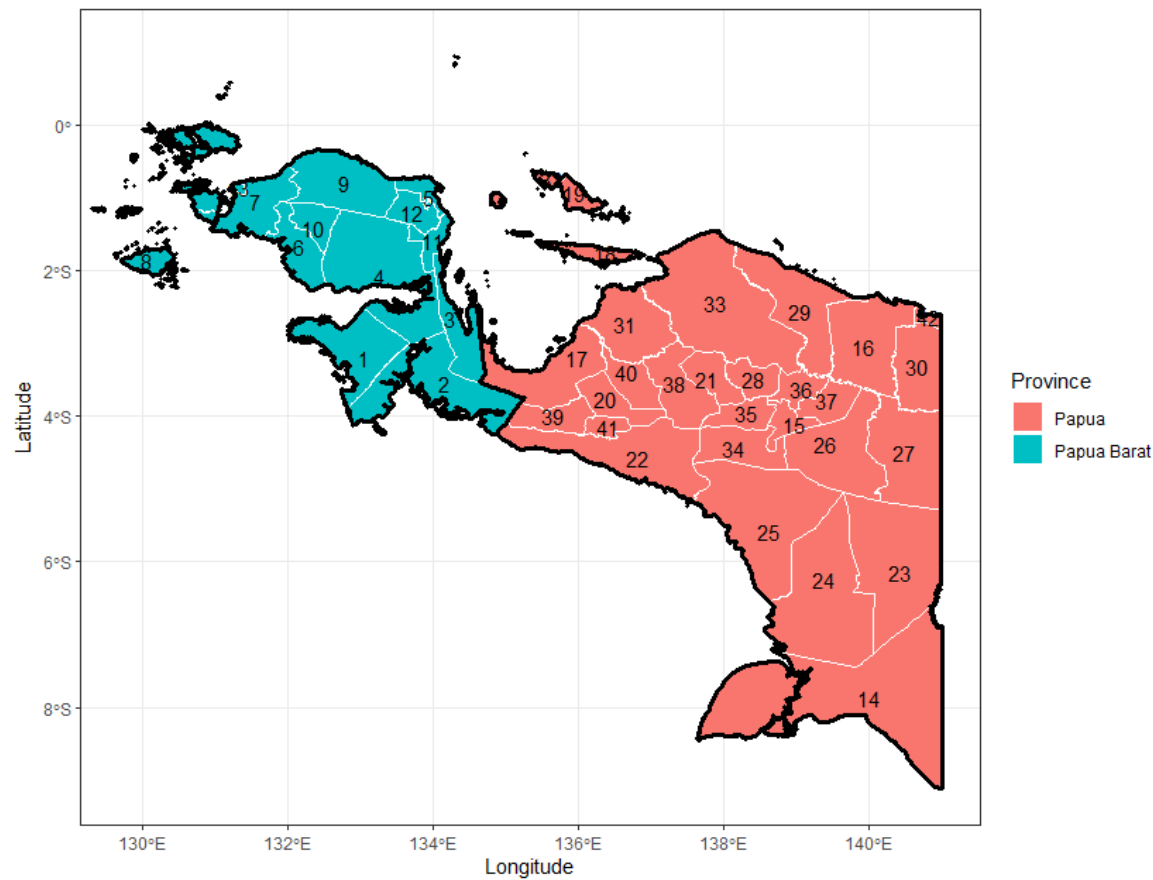


Figure S7.1. Districts in Papua Barat and Papua provinces. Name of the districts are listed in Table S1.

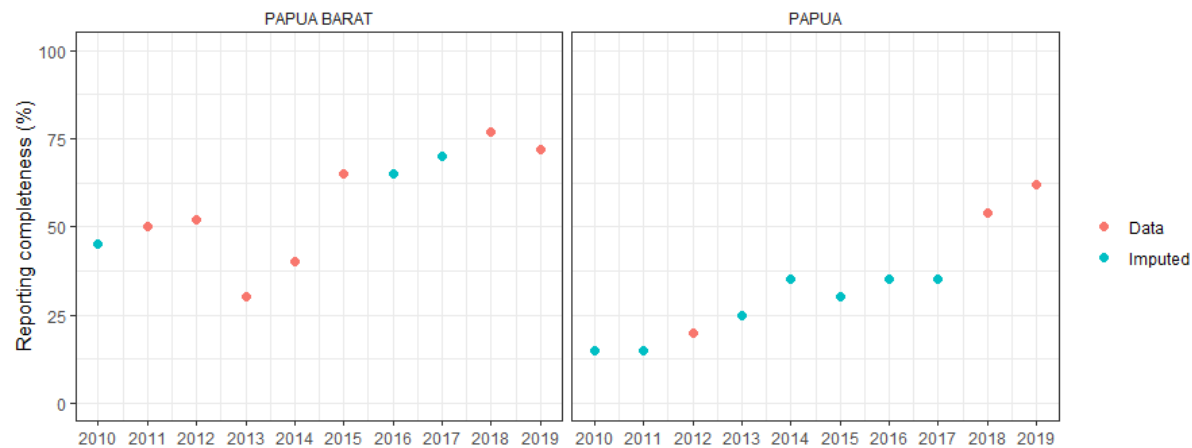


Figure S7.2. Province-level yearly reporting completeness of malaria routine data. Red dots denote data from routine surveillance and blue dots denote reasonable imputations for missing data of completeness.



Figure S7.3. District-level yearly reporting completeness of malaria routine data. Values in 2018 and 2019 are reported data while values in 2010 to 2017 are imputed and estimated data based on 2018-2019 average contribution to province-level reporting completeness.

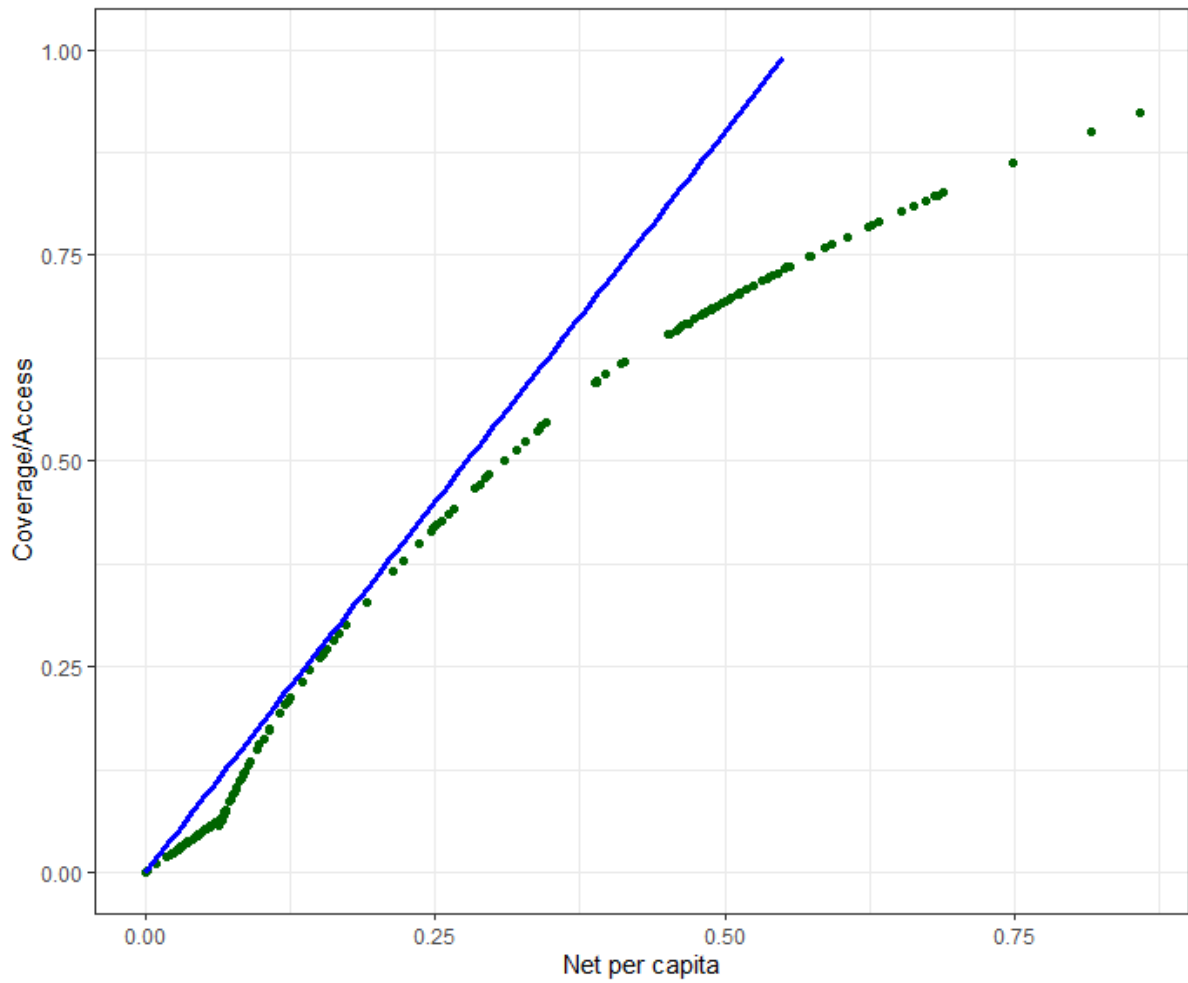


Figure S7.4. Plot of relationship between bednet metrics. Blue line denotes coverage ($1.8 \times \text{net per capita}$). Green points denote estimated access based on the relationship between net per capita and access in Bertozzi-Villa et al. Linear extrapolations with access:net per capita ratio = 1 were done when the value of net per capita is low.

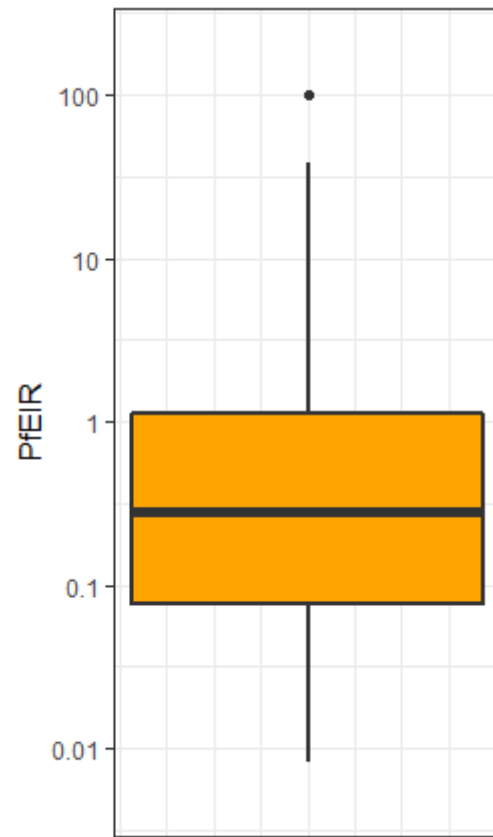


Figure S7.5. Distribution of initial PfEIR values used for model simulations. Y-axis at log-scale.

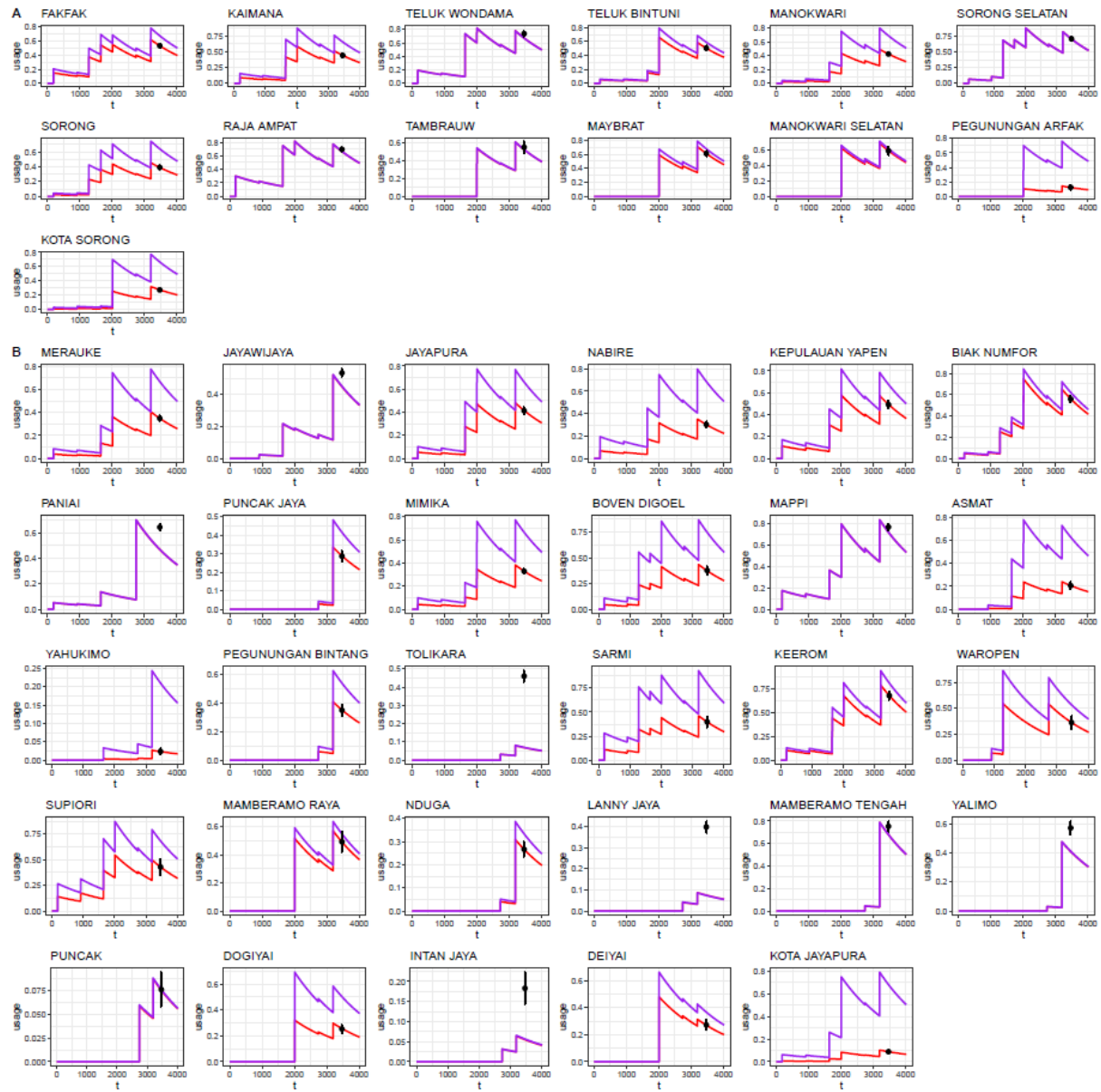


Figure S7.6. Modelled LLINs usage fitting to population LLINs usage proportion from 2018 surveys. X-axis is the timestep, and Y-axis itu the LLINs usage proportions. Purple lines denote modelled usage with 100% program effectiveness. Red lines denote modelled usage accounting for estimated program effectiveness, τ . **A)** Districts in Papua Barat province; and **B)** districts in Papua province.

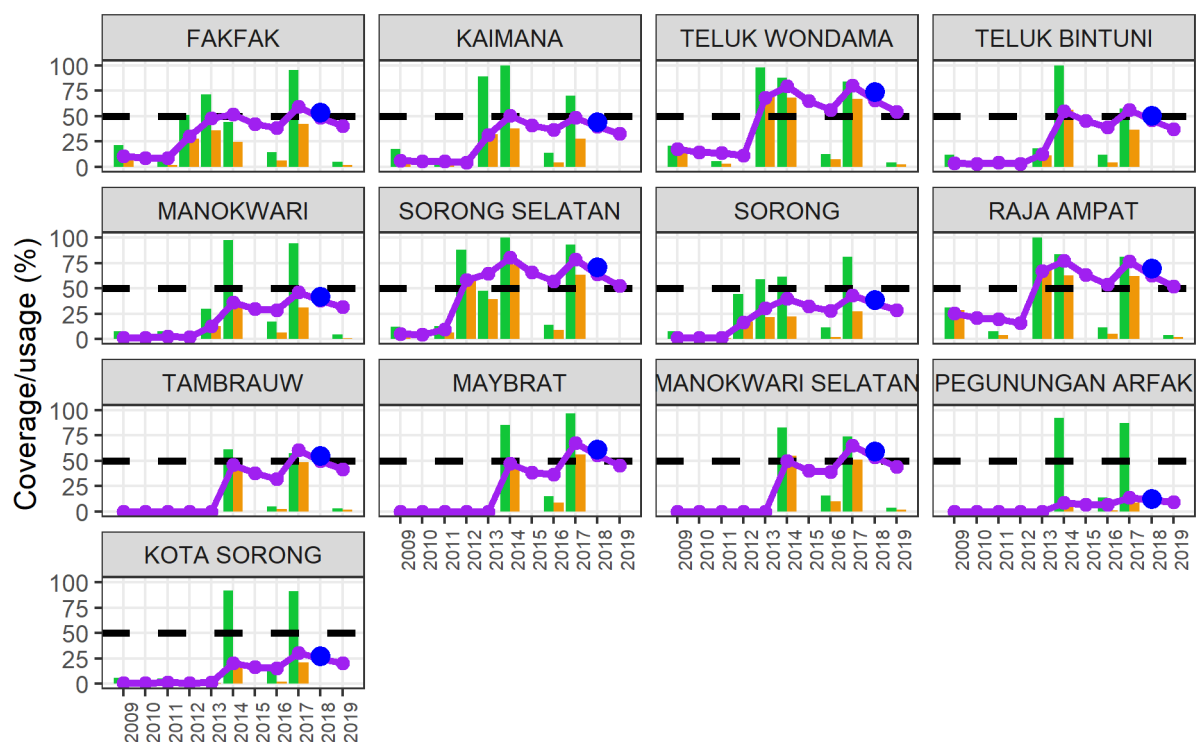


Figure S7.7. LLINs distribution coverages, based on the distribution data (green bars) and after LLIN usage model fitting to survey data (orange bars), the modelled usage based on the fitted coverages (purple lines), and the population LLIN usage survey data point of all districts in Papua Barat province.

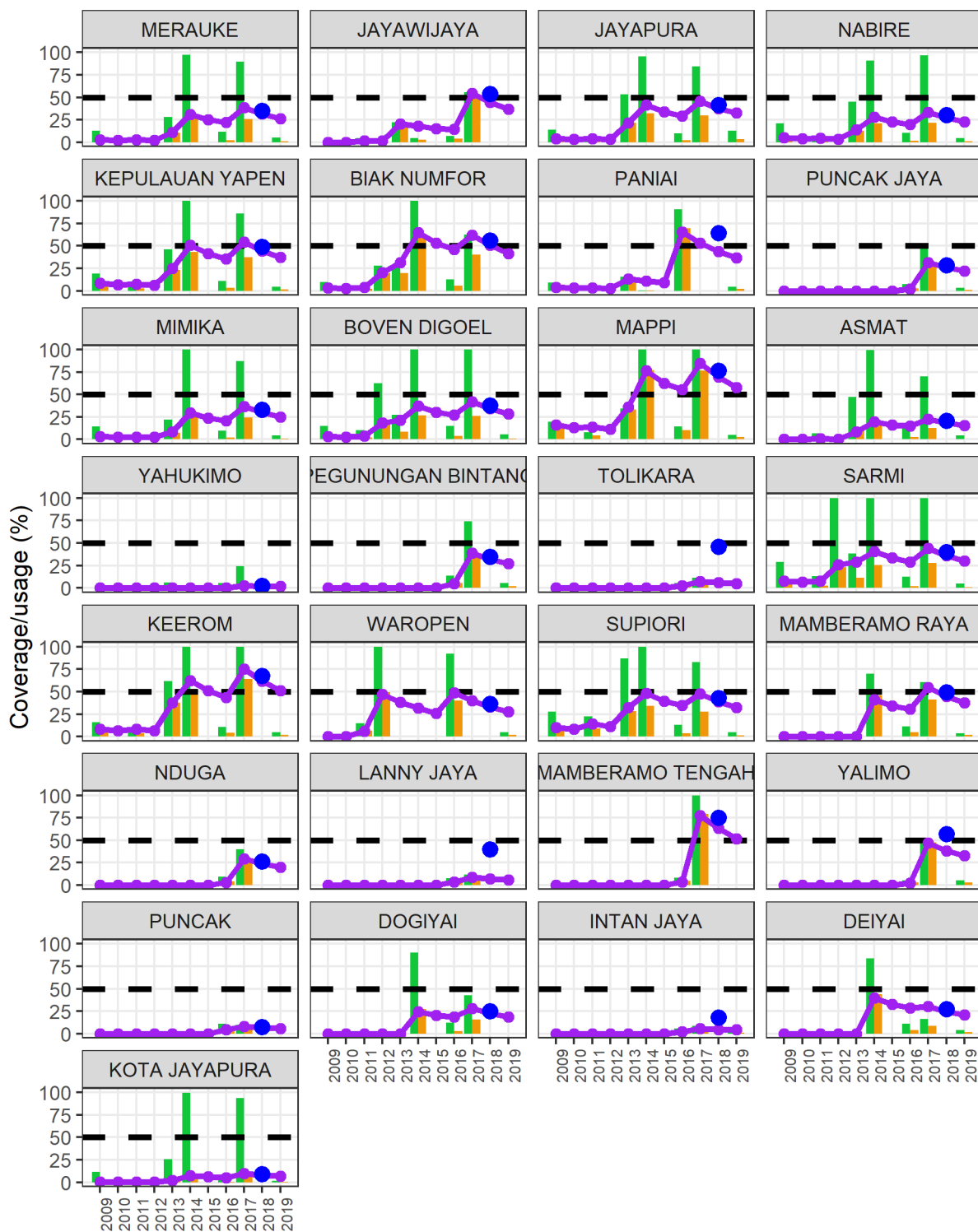


Figure S7.8. LLINs distribution coverages, based on the distribution data (green bars) and after LLIN usage model fitting to survey data (orange bars), the modelled usage based on the fitted coverages (purple lines), and the population LLIN usage survey data point of all districts in Papua province.

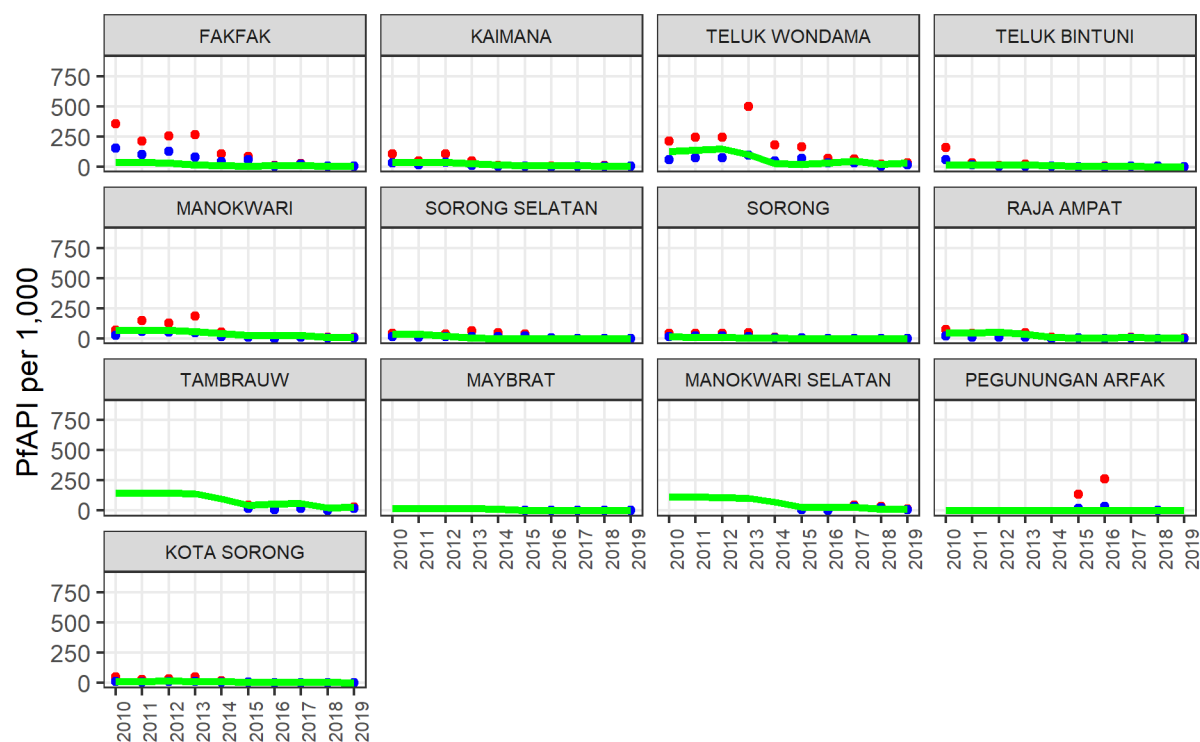


Figure S7.9. PfAPI per 1,000 based on reported data (blue), WHO-adjusted values (red), and model simulations (green) of all districts in Papua Barat province.

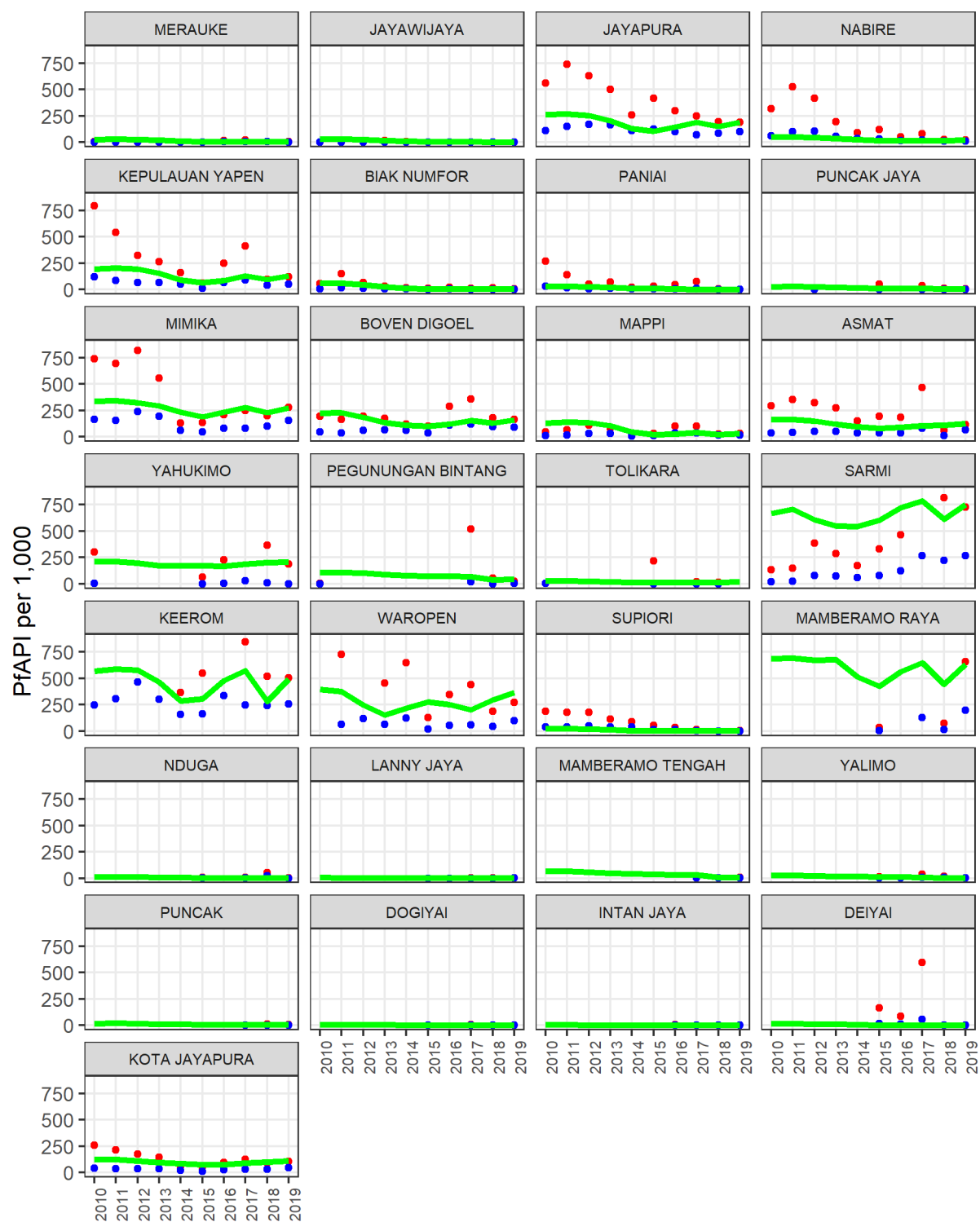


Figure S7.10. PfAPI per 1,000 based on reported data (blue), WHO-adjusted values (red), and model simulations (green) of all districts in Papua province.

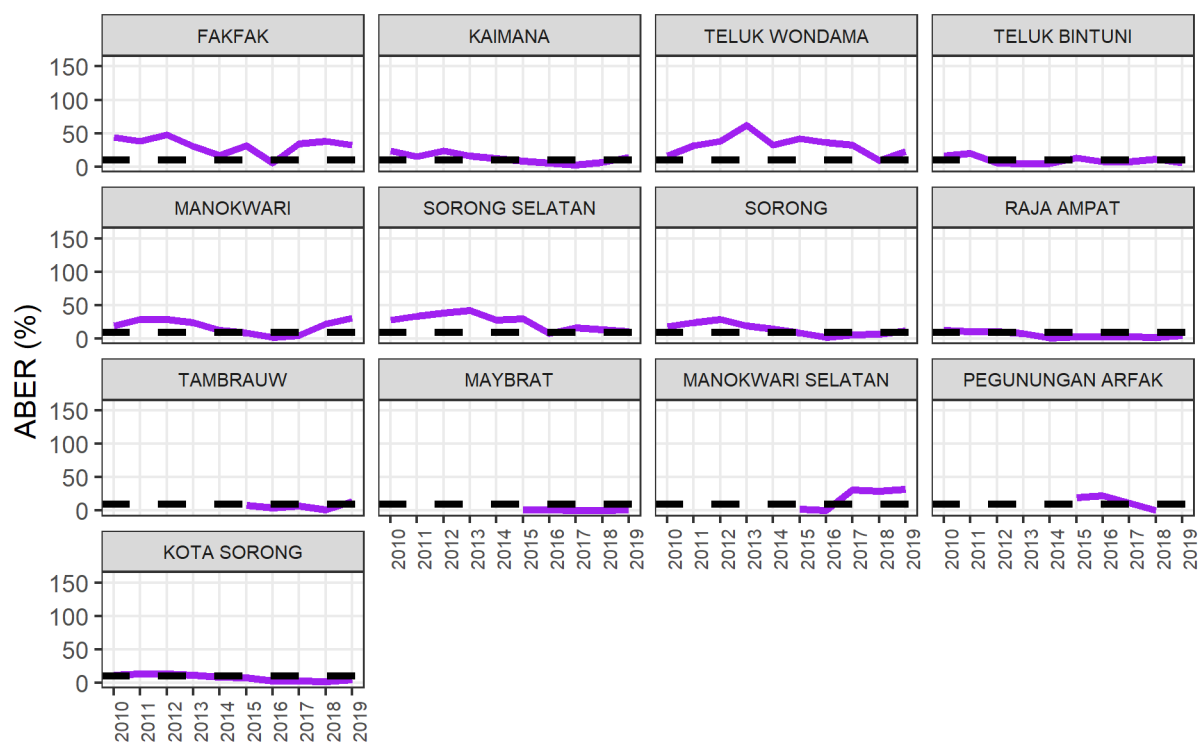


Figure S7.11. Annual Blood Examination Rate (ABER) of all districts in Papua Barat province. Dashed lines denote the 10% threshold of adequate ABER as per WHO standard.

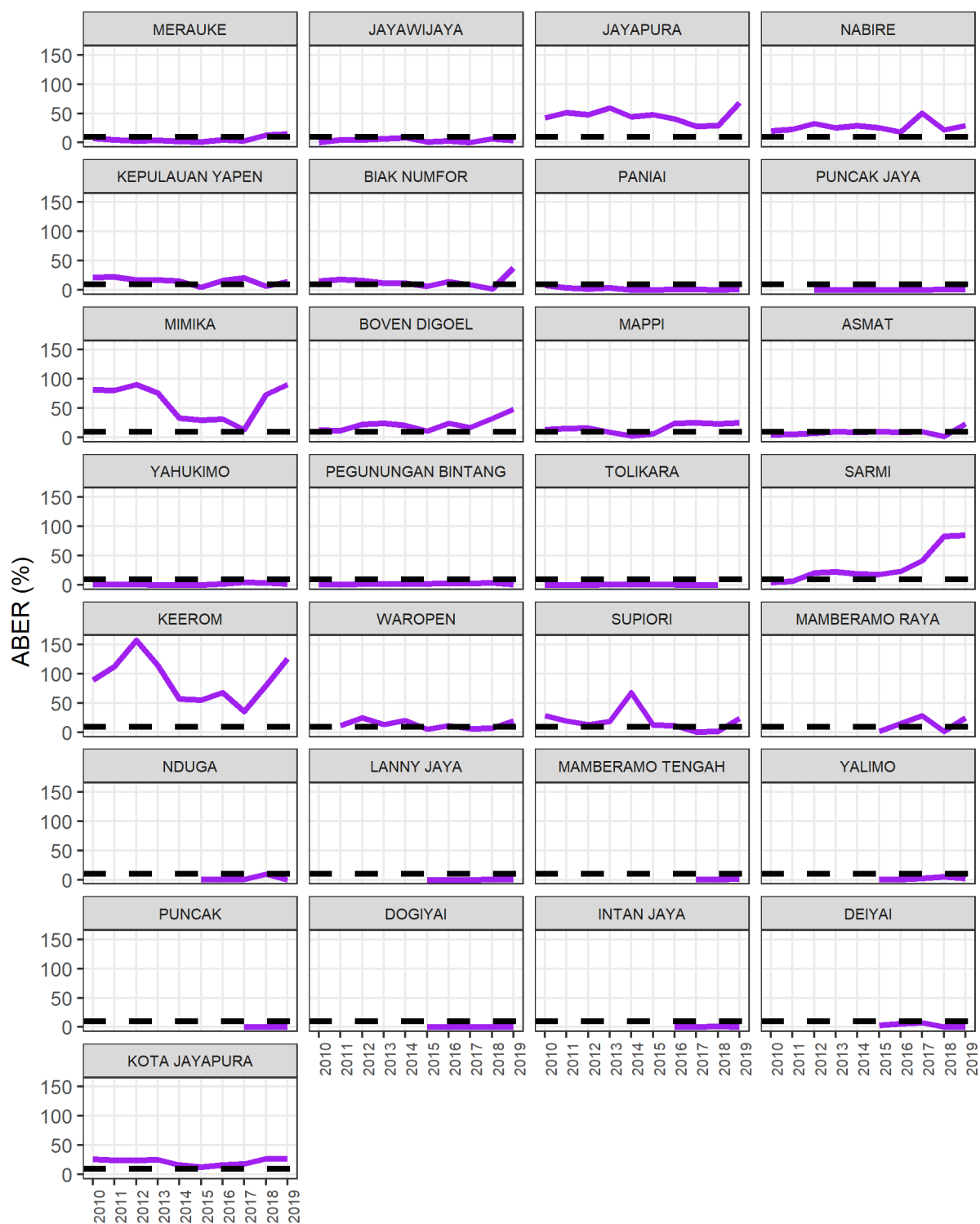


Figure S7.12. Annual Blood Examination Rate (ABER) of all districts in Papua province. Dashed lines denote the 10% threshold of adequate ABER as per WHO standard.

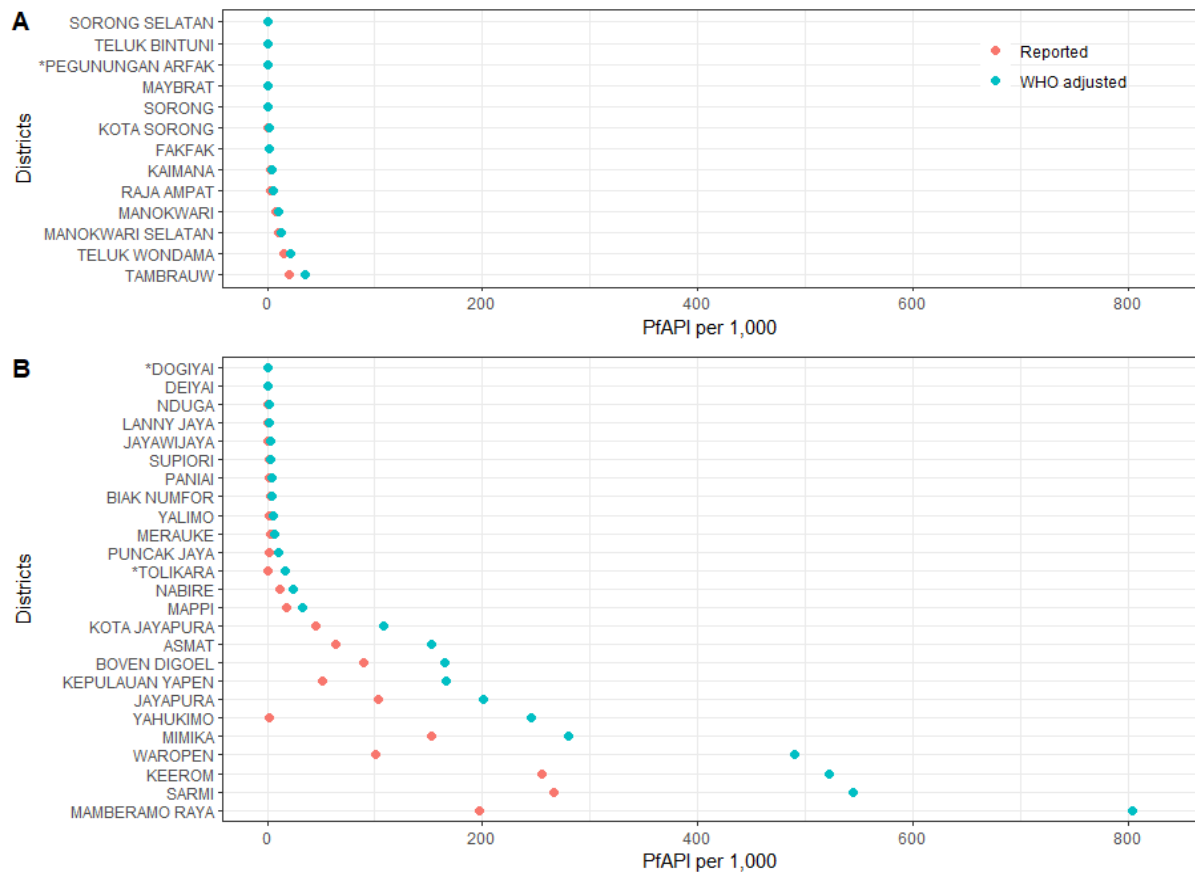


Figure S7.13. Comparison of reported *P. falciparum* incidence rates per 1,000 and their WHO-adjusted values in 2019. **A)** Districts in Papua Barat province; and **B)** districts in Papua province.