The incremental burden of invasive pneumococcal disease associated with a decline in childhood vaccination using a dynamic transmission model in Japan: A secondary impact of COVID-19

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A B S T R A C T

The coronavirus disease 2019 (COVID-19) pandemic has disrupted childhood vaccinations, including pneumococcal conjugate vaccine (PCV). Evaluating the possible impact on the invasive pneumococcal disease (IPD) incidence associated with a decline in childhood pneumococcal vaccination is important to advocate the PCV programs. Using a deterministic, dynamic transmission model, the differential incidence and burden of IPD in children younger than 5 years in Japan were estimated between the rapid vaccination recovery (January 2021) and the delayed vaccination recovery (April 2022) scenarios for the next 10 years. In our model, the IPD incidence was reduced from 11.9/100,000 in 2019 to 6.3/100,000 in 2020, caused by a reduced transmission rate due to the COVID-19 mitigation measures. Assuming a recovery in the transmission rate in 2022 April, the incidence of IPD was estimated to increase with maximal incidence of 12.1 and 13.1/100,000 children under 5 years in the rapid and the delayed vaccination recovery scenarios. The difference in the total IPD incidence between these two scenarios was primarily driven by vaccine serotypes IPD incidence. The difference of incidence was not observed between the two scenarios after 2025. The persistent decline in childhood pneumococcal vaccination rates due to the impact of COVID-19 might lead to an increased IPD incidence and an incremental disease burden.

1. Introduction

Pneumococcal infection is a vaccine-preventable disease (VPD) and represents a major cause of disease burden among children with invasive pneumococcal diseases (IPDs), including meningitis and bacteremia, associated with long-term sequelae or death [1]. Among more than 90 serotypes of *Streptococcus pneumoniae*, some of them are covered by pneumococcal vaccines. Since the introduction of pneumococcal conjugate vaccines (PCVs), many countries have achieved declines in the overall IPD incidence due to increases in both individual and herd immunity by high vaccination coverage, although increases in the incidence of IPD caused by non-vaccine serotypes (NVTs) have been reported [2–6]. Japan introduced 7-valent PCV (PCV7) in 2010, as voluntary vaccination, and PCV7 was officially included in the Japanese national immunization program as a routine vaccination starting in April 2013, with primary doses administered at 2, 3, and 4 months of age, followed by a booster dose administered at 12 months of age. This

vaccine was replaced by PCV13 in November 2013. The national PCV program has resulted in a 50%–60% reduction in IPD incidence among children younger than 5 years in Japan, with a significant serotype replacement (NVTs accounting for approximately 90% of IPDs in the post-vaccine era) [7,8].

However, since early 2020, many countries have suffered from disruptions in childhood vaccination programs, including pneumococcal vaccination, due to the outbreak of coronavirus disease 2019 (COVID-19), which has been declared as a global pandemic [9–13]. The pandemic has impacted vaccine supply and resulted in an increase in parents opting to cancel or postpone their children's vaccinations [14, 15]. Japan has reported that childhood vaccination coverage rates have dropped for infantile doses since early 2020 [16]. The ongoing decline in childhood vaccination rates represents a serious public health concern. Although a few studies have reported the impacts of declining childhood vaccination rates due to the COVID-19 pandemic [17–19], no study has evaluated the impact of this ongoing issue on IPD, with the

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consideration of the complexity associated with serotype replacement, to the best of our knowledge.

Evaluating the magnitude of the potential impacts on IPD and serotype distributions associated with the observed decline in childhood vaccinations during the COVID-19 pandemic is important to support PCV programs during the COVID-19 pandemic. Dynamic transmission models have been used to evaluate the dynamics of transmission, serotype replacement, and the incidence of IPD [20–24]. Because static models cannot accurately evaluate the impact of herd immunity or the dynamic change of infectious disease epidemiology over time, especially if the vaccination rate and the transmission rate are not stable over time, the dynamic transmission model is suitable to evaluate the transmission of IPD during and after the COVID-19 pandemic. Our objective was to evaluate the possible incremental impacts on IPD incidence among children under 5 years in Japan associated with a decline of childhood pneumococcal vaccination rates due to COVID-19, using a dynamic transmission model.

2. Materials and methods

2.1. Overview of the dynamic transmission model

A dynamic transmission model for IPD in Japan was developed to evaluate the differential impacts of a decrease in childhood pneumococcal vaccination from 2021 to 2030 due to the COVID-19 pandemic between the rapid and the delayed vaccination recovery scenarios. We developed a deterministic, susceptible-colonized-infected-recovered model (Fig. 1). First, the.

In this study, the disease burden of non-IPD was not considered due to a lack of timely epidemiological data regarding non-IPD, such as the incidence rates of non-invasive pneumonia and otitis media, during the COVID-19 outbreak. Whereas Japan has a national, weekly IPD surveillance system that was implemented in 2013 and is still in effect [25]. The model was divided into demographic and epidemiological components and programmed using Berkeley Madonna, version 8.3.18 (Berkeley, CA, USA), and Microsoft Excel 2016 (Redmond, WA, USA).

The rapid and delayed vaccination recovery scenarios were examined for the duration of vaccination rate decline to evaluate the

magnitude of the future impacts of COVID-19 on the IPD burden in Japan. Following a linear decline in the vaccination rate for the first half of 2020 in all scenarios, the rapid vaccination recovery scenario is defined as the recovery of vaccination rate starting January 2021 (irrespective of the duration of the impact of COVID-19 on the reduction of transmission rate), and the delayed vaccination recovery scenario refers to the recovery of vaccination rate when the impact of COVID-19 is over (April 2022 in the base case [26]). In the delayed vaccination recovery scenario, both the reduced transmission rate and the reduced vaccination rate were assumed to continue while the COVID-19 had impacts. On the other hand, in the rapid vaccination recovery scenario, only the reduced transmission rate was assumed to sustain during the COVID-19 impact period. Although past national declines in childhood vaccination rates have been associated with different durations [27–29], our study assumed the duration of declined vaccination in the delayed vaccination recovery scenario was correlated with the duration of reduced transmission rate by the impact of COVID-19. The duration of the impact of COVID-19 was investigated in the sensitivity analysis. The study outcomes included differences in the incidence of IPD and the cumulative loss of quality-adjusted life years (QALY) among children younger than 5 years between the rapid vaccination recovery and the delayed vaccination recovery scenarios. To calibrate the model, the reported incidence of IPD among 0–4-year-old children before the COVID-19 outbreak (2008–2019) were compared with the estimated incidence from the model run.

2.2. Demographic component

To simulate the real Japanese population, 11 age categories (0–2 month, 3–5 months, 6–11 months, 1 year, 2 years, 3 years, 4 years, 5–9 years, 10–19 years, 20–64 years, and ≥65 years) were created. All individuals were assumed to have 85 years of life expectancy [12,13]. Data regarding age-specific population dynamics during the study period were obtained from the national government [30,31].

2.3. Epidemiologic component

Fig. 1 shows the components of the epidemiologic model
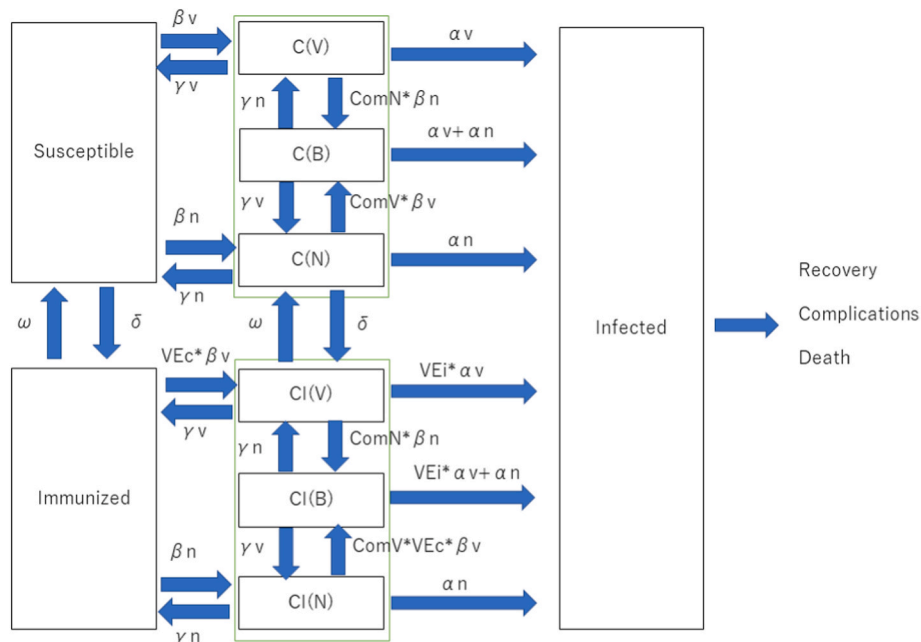
Fig. 1. Structure of the dynamic transmission model. α = attack rate of invasive pneumococcal disease (IPD) among a colonized population; β = transmission rate in a susceptible population; δ = vaccination rate; ω = immunity waning rate; ComV, ComN = competition rates; γ = rate of colonization clearance; VEc = vaccine effectiveness for colonization; VEi = vaccine effectiveness for IPD; V: vaccine serotype; N: non-vaccine serotype; B: both vaccine and non-vaccine serotypes.

(susceptible-colonized-infected-recovered). Serotypes were divided into vaccine serotypes (VTs) and NVTs. VTs consisted of the serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F, and all other serotypes were grouped into NVTs. Once a susceptible individual was exposed to *Streptococcus pneumoniae*, they could be moved to the colonized status, based on the transmission rate (β) and age-specific contact matrix. A small proportion of the colonized population developed IPD (attack rate = α). The infected individuals could then be moved to the recovered status, associated with permanent immunity, with a proportion that experienced death or permanent sequelae (Table 1).

Age-specific transmission rates and attack rates were calculated based on national surveillance reports regarding the colonization rate and IPD incidence, in combination with serotyping data [7,8,25,32–38]. Because limited data are available regarding the serotype distribution of colonization during the pre-vaccine era in Japan, the serotype distribution of colonization and IPD incidence for the post-vaccine period were used to estimate the serotype distribution of the pre-vaccine period. Attack rates were assumed to be stable over time. The relative contact rates, according to age, were calculated based on a previous Japanese study [39]. The duration of colonization was assumed to be 51 days for children under 5 years and 19 days for children 5 years or older [40]. The duration of colonization was assumed to be the same for both VT and NVT, as suggested by a previous study [41]. Studies regarding pneumococcal carriage have reported that two or more competing

Table 1
Parameters of the model.

		Base case	Reference
Vaccine coverage (primary/ booster doses)	2010–2012	0%–99.9%/0%–99.9%	[16,53,54]
	2013–2017	99.9%/99.9%	
	2018	98.0%/96.6%	
	2019	95.5%/95.2%	
	2020–	78.2%/61.3%	
Vaccine effectiveness for IPD[a]	Primary doses	86.0% (<12 months)	[47,49]
		69.9% (12–23 months)	
		23.3% (24–35 months)	
	Booster dose	90.3% for 5 years	
Vaccine effectiveness for colonization[b]		53%	[51]
Duration of colonization	<5 years	51 days	[40]
	5 years or older	19 days	
Initial VT rate in IPD		89.0%	[7]
Initial VT rate in colonization		84.6%	[7,37]
Initial colonization rate	0–5 months	17.3%	[25, 32–34]
	6–11 months	31.8%	
	12–23 months	48.0%	
	2–4 years	48.3%	
	5–19 years	42.3%	
	≥20 years	6.6%	
Average reported incidence of IPD (2008–2019)		25.0 and 12.2/100,000 person-years in the pre- and post-vaccine periods, respectively	[7,8,25, 32–38]
Case fatality rate		0.9%	[7,55,56]
Rate of meningitis in IPD cases		12.6%	
Rate of neurological sequelae in meningitis cases		18.8%	
Average QALY loss/case	Meningitis without sequelae	0.023	[55–60]
	Other IPD	0.008	
	Neurological sequelae	0.46/year	
Discount rate		3%	[61–63]

Initial status is the beginning status in the model (the year of 2008, the pre-vaccine period).
IPD: invasive pneumococcal disease; NVT: non-vaccine serotype; QALY: quality-adjusted life years; VT: vaccine serotype.
[a] PCV7 was assumed to be effective only for PCV7-covered serotype IPD and colonization.
[b] Vaccine effectiveness for colonization was assumed to wane with the same proportion to that for IPD.

serotypes could be detected in an individual [41]. In our model, an individual colonized with either VT or NVT could also be colonized with the other serotype group (VT and NVT co-colonization), using different competition parameters for a VT-colonized individual to be co-colonized with both VT and NVT ($ComN = 0.04$) and for a NVT-colonized individual to be co-colonized with both VT and NVT ($ComV = 0.5$) based on previous literature [24,42,43]. However, the degree of competition varied widely in each report; therefore, we performed a sensitivity analysis using a wide range of competition parameters (from 0 to 0.5) [24,43–45]. The parameters used in the model are presented in Table S1–S3, and the values obtained from each reference are presented in Table 1 and Table S4–6, respectively.

The infected individuals were assumed to be treated appropriately [21,24]. Therefore, transmission was only driven by a colonized population in the model. Equations used in the model are explained in Supplemental file.

A vaccinated individual was moved to the vaccinated status (Fig. 1). Although some variations in vaccine effectiveness have been reported by each study, multiple studies have reported the effectiveness of the 3 primary doses plus a booster dose (3 + 1) schedule as being approximately 85%–86% for the primary doses and 90%–91% for the booster dose [46–49]. In our model, the vaccine effectiveness of PCV13 for the prevention of VT IPD was assumed to be 86.0% for the primary doses and 90.3% for the booster dose [47]. This variation was explored in our sensitivity analysis using a vaccine effectiveness range of 75%–99% [46–50]. The vaccine effectiveness for colonization was assumed to be 53% in our model [51]. Although studies reported that children who received a booster dose had sustained vaccine effectiveness up to the age of 5 years [21,24,51,52], a previous study suggested that children who did not receive a booster dose had waning vaccine effectiveness over time [49]. In the base case of our model, children with a booster dose were assumed to have sustained vaccine effectiveness until 5 years of age, and the vaccine effectiveness among children without a booster dose waned (Table 1).

After the introduction of PCV7, the coverage rate demonstrated a linear increase during the transition phase (2010–2012), followed by the replacement of PCV7 with PCV13 in late 2013 [53]. Between 2013 and 2017, the vaccine coverage rate for PCV13 was estimated to be 99.9% for both primary and booster doses, followed by 98.0% and 96.6%, respectively, in 2018, and 95.5% and 95.2% in 2019 for the primary and booster doses (Table 1) [54]. The high coverage rate from 2013 to 2017 was due to the national data containing some catch-up vaccinations in the routine coverage rate [54]. Starting in January 2020, the coverage rate declined linearly for the next 6 months reaching 78.2% of primary doses and 61.3% of a booster dose in June 2020, based on a recent national report regarding the decline in the childhood vaccination rate [16]. This decline was estimated based on survey data collected using a national mobile vaccination app, which reported the monthly rates for the first dose of PCV13 coverage at 3 months of age, and the first dose of measles-rubella vaccine coverage at 14 months of age, among approximately 120,000 users from 2018 to June 2020 [16]. The coverage rate was estimated based on the number of users who answered that their children had already received the vaccine dose divided by the total number of users who were registered for the app with children of the same age. The relative reduction of the coverage rate in June 2020 compared to the previous year was calculated to estimate the magnitude of reduction in vaccinations. The first dose of the measles-rubella vaccine is typically administered at the same time as the PCV13 as part of the national immunization program. If vaccination rate recovery occurred in each scenario, a 6-month period was assumed to be necessary to recover to the levels observed during the pre-COVID-19 period. In the base case, we assumed that 50% of children less than 12 months who had missed vaccinations had catch-up vaccinations when the vaccination rate recovered. In our base-case scenario, this reduced transmission rate was assumed to recover at a linear rate over a 6-month period starting in July 2021, reaching the pre-COVID-19 transmission

rate starting in April 2022 [26]. However, because of the large degree of uncertainty regarding when the recovery of this reduced transmission rate would occur, we also performed a sensitivity analysis to analyze a wide range of durations for the reduced transmission rate, ranging from a rapid recovery (starting in January 2022) to a sustained reduction throughout the study period.

2.4. QALY component

The case fatality rate due to IPD was reported to be 0.9% [7]. Among IPD cases, 12.6% are reported to experience meningitis, and 18.8% of meningitis cases developed neurological sequelae, including hearing loss, epilepsy, developmental delay hydrocephalus, and paralysis [7,55, 56]. The average QALY loss per meningitis case without neurological sequelae and other IPD cases were assumed to be 0.023 and 0.008, respectively [57–59]. The average QALY loss per meningitis case with neurological sequelae was estimated to be 0.46, based on the responses to a national questionnaire [56]. We assumed that the average QALY per Japanese healthy person was 74 years [60]. The outcome tree model and the further explanation to calculate QALY are presented in Fig S1.

2.5. Model run and validation

The model run was conducted with the following steps. Using the age-specific Japanese population in 2008 and the data of colonization and IPD incidence in the pre-vaccine period, the initial population in each status of the model stratified by age group was calculated (Table S3), in which the year of 2008 was defined as the initiation of the model. Then, the model run was conducted to obtain the estimated incidence of IPD from 2008 to 2030. The model validation was conducted by comparing the reported incidence of IPD with the estimated incidence from the model run from 2008 to 2020.

2.6. Sensitivity analysis

The one-way sensitivity analysis was conducted to evaluate the uncertainty associated with the impact of COVID-19 on the incremental differences in QALY loss between the rapid recovery and delayed vaccination recovery scenarios during the 10-year-study period. The parameters included vaccine effectiveness (75%–99%), duration of vaccine effectiveness (3–10 years), competition rate (0–0.5), the minimal vaccination coverage rates during the COVID-19 period (50%–90% in the COVID-19 period for both primary and booster doses), the duration of the impact of COVID-19 (from 12 months to 10 years), and the discount rate (0%–6%) [61–63]. We also explored how much catch-up

vaccinations mitigate the incremental impact of delayed vaccination recovery if all children 12 months or younger who had missed vaccinations in the delayed vaccination recovery scenario received catch-up doses when the impact of COVID-19 was over in April 2022.

3. Results

Fig. 2 shows the incidence of IPD/100,000 children younger than 5 years estimated by our model over the entire study period, compared with the actually reported incidence [7,8,25,38]. During the pre-vaccine period (2008–2010), the average incidence estimated by our model was 25.5/100,000 children younger than 5 years, whereas the actual average incidence during the same period was reported to be 25.0/100, 000 children younger than 5 years. During the post-vaccine, pre-COVID-19 period (2014–2019), the average incidence estimated by the model was reduced to 11.8/100,000 children younger than 5 years, whereas the reported average incidence was 12.2/100,000 children younger than 5 years (Fig. 2). Over the post-vaccine, pre-COVID-19 period, VT IPD was gradually replaced by NVT IPD.

In 2020, both the transmission rate and the vaccine coverage rate were reduced due to the impacts of COVID-19. The reduction in the IPD transmission rate during the COVID-19 outbreak was calculated as 26% by calibrating our model using the weekly national IPD surveillance data until the end of 2020 and comparing against the data reported for 2019 [25]. Both the model-estimated and reported incidence reduced to 6.4/100,000 children younger than 5 years by the end of 2020. Assuming a recovery in the transmission rate in 2022 April, the incidence of IPD was estimated to increase with maximal incidence of 12.1 (VT IPD 1.6 and NVT IPD 10.5) and 13.1 (VT IPD 3.1 and NVT IPD 10.1)/100,000 children under 5 years in 2023 in the rapid and the delayed vaccination recovery scenarios (Fig. 2). The difference in total IPD incidence between the rapid and the delayed vaccination recovery scenarios was primarily driven by the difference in the estimated VT IPD incidence (Fig. 2). The incidence in the delayed recovery scenario started decreasing in late 2023 due to the improved vaccination rate, and the difference of incidence was not observed between the two scenarios after late 2025. The average incidence of IPD was 12.1 (VT IPD 1.4 and NVT IPD 10.6)/100,000 children under 5 years between July 2025 and December 2030 in both the rapid and the delayed vaccination recovery scenarios. With the COVID-19 impact until April 2022, the delayed vaccination recovery scenario had 82.7 incremental QALY loss between 2021 and 2025 compared to the rapid vaccination recovery scenario (Table 2).

Fig. 3 shows the one-way sensitivity analysis. Among the 6 parameters, the duration of the COVID-19 impact, followed by the reduced
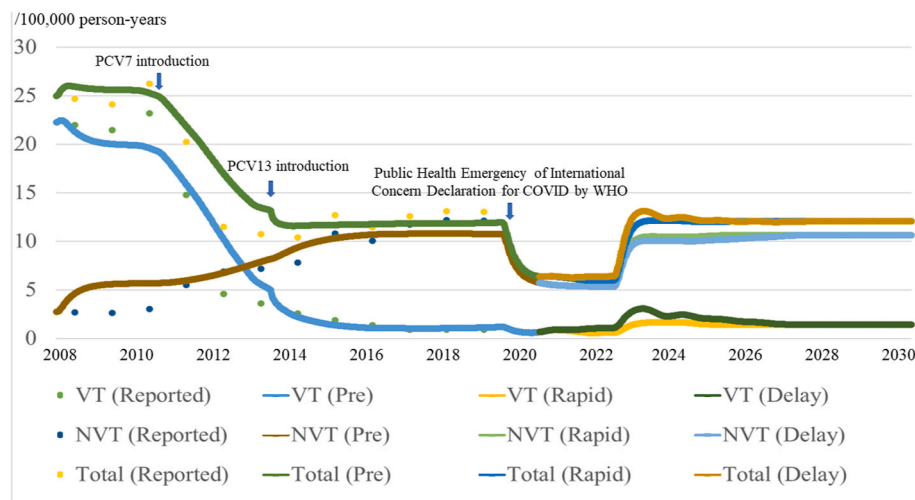

Fig. 2. Incidence of invasive pneumococcal diseases under 5 years old From January 2020 to June 2020 pneumococcal vaccination rates reduced linearly, to 78.2% and 61.3% for primary and booster doses, respectively. The relative reduction in pneumococcal transmission rates was estimated to be 26% from January 2020 to June 2021. A recovery from the reduced vaccination rates was assumed to occur during the 6 months from January 2021 to June 2021 for the rapid vaccination recovery scenario and from April 2022 to September 2022 for the delayed vaccination recovery scenario. Recovery of the reduced transmission rate was assumed to occur in April 2022 for both scenarios.

PCV: pneumococcal conjugate vaccine; VT: vaccine serotype; NVT: non-vaccine serotype; Rapid: rapid vaccination recovery scenario; Delayed: delayed vaccination recovery scenario.

Table 2

The cumulative, incremental QALY loss of invasive pneumococcal disease in children under 5 years old in the delayed vaccination recovery scenario compared with the rapid vaccination recovery scenario due to the impacts of COVID-19 on vaccination rates since January 2021.

	QALY loss
1 year (until the end of 2021)	2.89
2 years (until the end of 2022)	39.6
3 years (until the end of 2023)	67.2
4 years (until the end of 2024)	78.5
5 years (until the end of 2025)	82.7

QALY: quality-adjusted life year; Discount rate = 3%.

Fig. 3. Sensitivity analysis The cumulative incremental quality-adjusted life-year (QALY) loss for the delayed vaccination recovery scenario compared with the rapid vaccination recovery scenario over the next 10 yearsOne-way sensitivity analyses were performed for the following ranges of each factor: vaccine effectiveness, 75%–99%; duration of vaccine effectiveness, 3–10 years; serotype competition rate, 0–0.5; the reduced vaccination coverage rates during the COVID-19 period, 50%–90% during the COVID-19 period for primary and booster doses; the duration of the impact of COVID-19, 12 months–10 years; and the discount rate, 0%–6%. The horizontal line for each the box indicates the incremental QALY loss from the base case.
Abbreviation: QALY, quality-adjusted life years.

vaccine coverage rate during the COVID-19 period, was the most sensitive for the cumulative incremental QALY loss between the rapid and the delayed vaccination recovery in the scenarios. If all children 12 months or younger who had missed vaccinations in the delayed vaccination recovery scenario received catch-up doses when the impact of COVID-19 was over in April 2022, the differential QALYs loss between the rapid and delayed vaccination recovery scenarios between 2021 and 2030 was estimated to reduce by 10.4%.

4. Discussion

The study highlights the estimated incremental IPD disease burden and the increase in the VT IPD incidence among children younger than 5 years if the decline in vaccination rates due to COVID-19 persists. The rapid recovery and shortened duration of the decline in vaccination rates is crucial for the prevention of an incremental disease burden in the future.

Because of serotype replacements after PCV introduction, some articles have argued the necessity and beneficial effects of maintaining high childhood pneumococcal vaccination rates among these populations [64,65]. Our study showed that a decrease in the childhood

pneumococcal vaccination rate was associated with a resurgence in the VT IPD incidence rate. The increased incidence of VT IPD, up to 3.1/100, 000 children younger than 5 years, appeared to be relatively small compared with the VT IPD incidence rate in the pre-vaccine era, which was approximately 20/100,000 children younger than 5 years. This difference may be because of sustained herd immunity. However, maintaining a high rate of vaccination coverage is important, even though some highly vaccinated countries have ceased to observe continued reductions in IPD incidence.

Our model calibration estimated a 26% reduction in the pneumococcal transmission rate due to COVID-19 mitigation measures in 2020. Although some surveys have reported significant reductions in the incidence of non-COVID-19 respiratory infections in 2020, few data are available regarding the magnitude of reductions in the transmission rates, rather than the incidence rates, of non-COVID-19 respiratory infections [66–70]. Evaluating the magnitude of reduced transmission rates for infectious diseases other than COVID-19 in repose to the enactment of COVID-19 mitigation measures is also important for better understanding infectious disease epidemiology in the COVID-19 eras.

Our study is limited by the large degree of uncertainty regarding how long the COVID-19 will impact the observed reductions in childhood vaccination rates and disease transmission rates. We also assumed that the vaccination rate of the first dose could be applied to the rest of primary doses. We performed sensitivity analyses using wide ranges of these parameters. Because of the nature of our dynamic transmission model, we could not capture annual fluctuations in the IPD incidence rate in our model. Although the actual incidence established by national reports revealed variability in the annual IPD incidence rates and the proportions of VT vs. NVT strains during the same periods (pre-vaccine or post-vaccine period), our model reported a stable IPD incidence, which may result in differences between the incidence estimated by our model run and the actual incidence in any given year. However, we believe that this does not compromise the overall trend displaying the likely differences in the IPD incidence and disease burden between the rapid and the delayed vaccination recovery scenarios. Finally, because simulating all pneumococcal serotypes is impossible, we grouped serotypes, as has been described for other pneumococcal modeling studies. Therefore, our model is unable to assess the effects of an individual that is simultaneously colonized by more than one VT strain, more than one NVT strain, or more than 2 serotypes.

In conclusion, a persistent decline in the childhood pneumococcal vaccination rate due to the impacts of COVID-19 could result in an increase in the IPD incidence and an incremental disease burden. These increases are primarily because of an increase in VT IPD. A rapid recovery in the vaccination coverage rate could prevent this possible increase in the disease burden. Sustaining a high pneumococcal vaccination rate is important for minimizing the disease burden of childhood IPD, even though the impact of vaccination appears to be minimal due to serotype replacement.

Authors' contributions

All authors meet the ICMJE criteria for authorship. T. Kitano and H. Aoki designed the study. T. Kitano and H. Aoki conducted the literature review. T. Kitano conducted the study, and wrote the first manuscript. H. Aoki critically reviewed the paper. All authors approved to submit the final version.

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Declaration of competing interest

There is no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.compbiomed.2021.104429.

References

[1] K.L. O'Brien, L.J. Wolfson, J.P. Watt, E. Henkle, M. Deloria-Knoll, N. McCall, et al., Burden of disease caused by Streptococcus pneumoniae in children younger than 5 years: global estimates, Lancet 374 (2009) 893–902.

[2] C.G. Whitney, M.M. Farley, J. Hadler, L.H. Harrison, N.M. Bennett, R. Lynfield, et al., Active bacterial core surveillance of the emerging infections program network. Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine, N. Engl. J. Med. 348 (2003) 1737–1746.

[3] P. Izurieta, P. Bahety, R. Adegbola, C. Clarke, B. Hoet, Public health impact of pneumococcal conjugate vaccine infant immunization programs: assessment of invasive pneumococcal disease burden and serotype distribution, Expert Rev. Vaccines 17 (2018) 479–493.

[4] J. Ruiz-Contreras, J. Picazo, J. Casado-Flores, F. Baquero-Artigao, T. Hernández-Sampelayo, E. Otheo, et al., Impact of 13-valent pneumococcal conjugate vaccine on pneumococcal meningitis in children, Vaccine 35 (35 Pt B) (2017) 4646–4651.

[5] C. Levy, N. Ouldali, L. Caeymaex, F. Angoulvant, E. Varon, R. Cohen, Diversity of serotype replacement after pneumococcal conjugate vaccine implementation in Europe, J. Pediatr. 213 (2019), 252-3.e3.

[6] C.L. Gaviria-Agudelo, A. Jordan-Villegas, C. Garcia, G.H. McCracken Jr., The effect of 13-valent pneumococcal conjugate vaccine on the serotype distribution and antibiotic resistance Profiles in children with invasive pneumococcal disease, J Pediatric Infect Dis Soc 6 (2017) 253–259.

[7] S. Suga, B. Chang, K. Asada, H. Akeda, J. Nishi, K. Okada, et al., Nationwide population-based surveillance of invasive pneumococcal disease in Japanese children: effects of the seven-valent pneumococcal conjugate vaccine, Vaccine 33 (2015) 6054–6060.

[8] K. Ubukata, M. Takata, M. Morozumi, N. Chiba, T. Wajima, S. Hanada, et al., Effects of pneumococcal conjugate vaccine on genotypic Penicillin resistance and serotype changes, Japan, 2010-2017, Emerg. Infect. Dis. 24 (2018) 2010–2020.

[9] C.A. Bramer, L.M. Kimmins, R. Swanson, J. Kuo, P. Vranesich, L.A. Jacques-Carroll, et al., Decline in Child Vaccination Coverage during the COVID-19 Pandemic - Michigan Care Improvement Registry, May 2016-May 2020. MMWR Morb Mortal Wkly Rep, vol. 69, 2020, pp. 630–631.

[10] N.E. MacDonald, J.L. Comeau, È. Dubé, L.M. Bucci, COVID-19 and missed routine immunizations: designing for effective catch-up in Canada, Can. J. Public Health 111 (2020) 469–472.

[11] A.A. Adamu, R.I. Jalo, D. Habonimana, C.S. Wiysonge, COVID-19 and routine childhood immunization in Africa: leveraging systems thinking and implementation science to improve immunization system performance, Int. J. Infect. Dis. 98 (2020) 161–165.

[12] S. Chandir, D.A. Siddiqi, M. Mehmood, H. Setayesh, M. Siddique, A. Mirza, et al., Impact of COVID-19 pandemic response on uptake of routine immunizations in Sindh, Pakistan: an analysis of provincial electronic immunization registry data, Vaccine 38 (2020) 7146–7155.

[13] M. Alsuhaibani, A. Alaqeel, Impact of the COVID-19 pandemic on routine childhood immunization in Saudi Arabia, Vaccines (Basel) 8 (2020) E581.

[14] S. Saxena, H. Skirrow, H. Bedford, Routine vaccination during covid-19 pandemic response, BMJ 369 (2020) m2392, https://doi.org/10.1136/bmj.m2392.

[15] H.I. McDonald, E. Tessier, J.M. White, M. Woodruff, C. Knowles, C. Bates, et al., Early impact of the coronavirus disease (COVID-19) pandemic and physical distancing measures on routine childhood vaccinations in England, January to April 2020, Euro Surveill. 25 (2020) 2000848, https://doi.org/10.2807/1560-7917.ES.2020.25.19.2000848.

[16] Know VPD! Protect Our Children. Release: Decreased Childhood Vaccination Rate Due to COVID-19 Outbreak, 2020 (Japanese), https://www.know-vpd.jp/news/20741.php. (Accessed 28 June 2020).

[17] K. Abbas, S.R. Procter, K. van Zandvoort, A. Clark, S. Funk, T. Mengistu, et al., Routine childhood immunisation during the COVID-19 pandemic in Africa: a benefit-risk analysis of health benefits versus excess risk of SARS-CoV-2 infection, Lancet Glob Health 8 (2020) e1264–e1272.

[18] T. Kitano, H. Aoki, The estimated impact of decreased childhood vaccination due to COVID-19 using a dynamic transmission model of mumps in Japan, Hum. Vaccines Immunother. (2020 Oct 29) 1–4, https://doi.org/10.1080/21645515.2020.1826799.

[19] T. Kitano, H. Aoki, A model for the incremental burden of invasive Haemophilus influenzae type b due to a decline of childhood vaccination during the COVID-19 outbreak: A dynamic transmission model in Japan, Vaccine 39 (2021) 343–349.

[20] A. Løchen, R.M. Anderson, Dynamic transmission models and economic evaluations of pneumococcal conjugate vaccines: a quality appraisal and limitations, Clin. Microbiol. Infect. 26 (2020) 60–70.

[21] M. Wasserman, A. Lucas, D. Jones, M. Wilson, B. Hilton, A. Vyse, H. Madhava, A. Brogan, M. Slack, R. Farkouh, Dynamic transmission modelling to address infant pneumococcal conjugate vaccine schedule modifications in the UK, Epidemiol. Infect. 146 (2018) 1797–1806.

[22] E. Gjini, M.G.M. Gomes, Expanding vaccine efficacy estimation with dynamic models fitted to cross-sectional prevalence data post-licensure, Epidemics 14 (2016) 71–82.

[23] C. Bottomley, A. Roca, P.C. Hill, B. Greenwood, V. Isham, A mathematical model of serotype replacement in pneumococcal carriage following vaccination, J. R. Soc. Interface 10 (2013) 20130786.

[24] E. De Cao, A. Melegaro, R. Klok, M. Postma, Optimising assessments of the epidemiological impact in The Netherlands of paediatric immunisation with 13-valent pneumococcal conjugate vaccine using dynamic transmission modelling, PloS One 9 (2014), e89415.

[25] National Institute of Infectious Diseases, Infectious disease surveillance weekly report. https://www.niid.go.jp/niid/en/. (Accessed 2 December 2020).

[26] Airfinity. Snapshot COVID-19 data. https://www.ifpma.org/wp-content/uploads/2020/12/Airfinity-final-slides.pdf. (Accessed 22 February 2021).

[27] T. Nakayama, Vaccine chronicle in Japan, J. Infect. Chemother. 19 (2013) 787–798.

[28] National Institute of Infectious Diseases, Japanese encephalitis vaccine supply system, Infectious Agents Surveillance Report IASR 38 (2017) 165–166 (Japanese), https://www.niid.go.jp/niid/ja/typhi-m/iasr-reference/2410-related-articles/related-articles-450/7470-450r10.html. (Accessed 2 December 2020).

[29] T. Kitano, Close the gap for routine mumps vaccination in Japan, Hum. Vaccines Immunother. 12 (2020) 1–6.

[30] Statistics Bureau, ministry of internal affairs and communications. Statistics Japan, statistical yearbook 2020. Tokyo. http://www.stat.go.jp/english/index.htm. (Accessed 2 December 2020).

[31] Cabinet Office, Government of Japan, The State of Population Aging, 2017. Tokyo, http://www8.cao.go.jp/kourei/whitepaper/w-2016/html/zenbun/s1_1_1.html. (Accessed 2 December 2020).

[32] T. Otsuka, B. Chang, T. Shirai, A. Iwaya, A. Wada, N. Yamanaka, et al., Individual risk factors associated with nasopharyngeal colonization with Streptococcus pneumoniae and Haemophilus influenzae: a Japanese birth cohort study, Pediatr. Infect. Dis. J. 32 (7) (2013 Jul) 709–714.

[33] K. Hashida, T. Shiomori, N. Hohchi, T. Kitamura, T. Udaka, H. Suzuki, Survey of Nasopharyngeal Carriage of Haemophilus Influenzae and Streptococcus Pneumoniae in Infants at Day Care Centers. (Japanese) Nihon Jibiinkoka Gakkai Kaiho, vol. 109, 2006, pp. 821–829.

[34] R. Nagata, Examination of the resistance trend of nasopharynx origin Streptococcus pneumoniae in a normal child and adult, J. Juzen Med. Soc. 115 (2006) 75–85.

[35] National institute of infectious diseases. Bacterial meningitis 2006-2011. https://www.niid.go.jp/niid/ja/corynebacterium-m/corynebacterium-idwrs/2113-idwrs-1216.html. (Accessed 2 December 2020).

[36] Ministry of Health, Labour and Welfare of Japan, Research for surveillance system establishment, analysis of pathophysiology, diagnosis and treatment of severe streptococcal and pneumococcal infections (Japanese), http://strep.umin.jp/pneumococcus/case_study.html. (Accessed 3 December 2020).

[37] B. Chang, H. Akeda, Y. Nakamura, H. Hamabata, K. Ameku, T. Toma, et al., Impact of thirteen-valent pneumococcal conjugate vaccine on nasopharyngeal carriage in healthy children under 24 months in Okinawa, Japan, J. Infect. Chemother. 26 (2020) 465–470.

[38] S. Nakano, T. Fujisawa, Y. Ito, B. Chang, Y. Matsumura, M. Yamamoto, et al., Nationwide surveillance of paediatric invasive and non-invasive pneumococcal disease in Japan after the introduction of the 13-valent conjugated vaccine, 2015-2017, Vaccine 38 (7) (2020 Feb 11) 1818–1824.

[39] L. Munasinghe, Y. Asai, H. Nishiura, Quantifying heterogeneous contact patterns in Japan: a social contact survey, Theor. Biol. Med. Model. 16 (2019) 6.

[40] A. Melegaro, N.J. Gay, G.F. Medley, Estimating the transmission parameters of pneumococcal carriage in households, Epidemiol. Infect. 132 (2004) 433–441.

[41] S. Cauchemez, L. Temime, A.J. Valleron, E. Varon, G. Thomas, D. Guillemot, et al., S. pneumoniae transmission according to inclusion in conjugate vaccines: Bayesian analysis of a longitudinal follow-up in schools, BMC Infect. Dis. 6 (2006) 14.

[42] S.D. Brugger, L.J. Hathaway, K. Mühlemann, Detection of Streptococcus pneumoniae strain cocolonization in the nasopharynx, J. Clin. Microbiol. 47 (2009) 1750–1756.

[43] Y.H. Choi, M. Jit, N. Gay, N. Andrews, P.A. Waight, et al., 7-Valent pneumococcal conjugate vaccination in England and Wales: is it still beneficial despite high levels of serotype replacement? PloS One 6 (2011), e26190.

[44] A. Melegaro, Y. Choi, R. Pebody, N. Gay, Pneumococcal carriage in United Kingdom families: estimating serotype-specific transmission parameters from longitudinal data, Am. J. Epidemiol. 166 (2007) 228–335.

[45] E. Gjini, Geographic variation in pneumococcal vaccine efficacy estimated from dynamic modeling of epidemiological data post-PCV7, Sci. Rep. 7 (2017) 3049.

[46] M. van der Linden, G. Falkenhorst, S. Perniciaro, C. Fitzner, M. Imöhl, Effectiveness of pneumococcal conjugate vaccines (PCV7 and PCV13) against invasive pneumococcal disease among children under two years of age in Germany, PloS One 11 (2016), e0161257.

[47] M.R. Moore, R. Link-Gelles, W. Schaffner, R. Lynfield, C. Holtzman, L.H. Harrison, et al., Effectiveness of 13-valent pneumococcal conjugate vaccine for prevention of invasive pneumococcal disease in children in the USA: a matched case-control study, Lancet Respir Med 4 (2016) 399–406.

[48] M. Berman-Rosa, S. O'Donnell, M. Barker, C. Quach, Efficacy and effectiveness of the PCV-10 and PCV-13 vaccines against invasive pneumococcal disease, Pediatrics 145 (2020), e20190377.

[49] S. Jayasinghe, C. Chiu, H. Quinn, R. Menzies, R. Gilmour, P. McIntyre, Effectiveness of 7- and 13-valent pneumococcal conjugate vaccines in a schedule without a booster dose: a 10-year observational study, Clin. Infect. Dis. 67 (2018) 367–374.

[50] N.J. Andrews, P.A. Waight, P. Burbidge, E. Pearce, L. Roalfe, M. Zancolli, et al., Serotype-specific effectiveness and correlates of protection for the 13-valent pneumococcal conjugate vaccine: a postlicensure indirect cohort study, Lancet Infect. Dis. 14 (9) (2014 Sep) 839–846.

[51] J.A. Lewnard, N. Givon-Lavi, R. Dagan, Dose-specific effectiveness of 7- and 13-valent pneumococcal conjugate vaccines against vaccine-serotype Streptococcus pneumoniae colonization in children, Clin. Infect. Dis. 71 (8) (2020 Nov 5) e289–e300.

[52] Y.H. Choi, M. Jit, S. Flasche, N. Gay, E. Miller, Mathematical modelling long-term effects of replacing Prevnar7 with Prevnar13 on invasive pneumococcal diseases in England and Wales, PloS One 7 (2012), e39927.

[53] N. Chiba, M. Morozumi, M. Shouji, T. Wajima, S. Iwata, K. Ubukata, Changes in capsule and drug resistance of Pneumococci after introduction of PCV7, Japan, 2010-2013, Emerg. Infect. Dis. 20 (2014) 1132–1139.

[54] Ministry of Health, Labour and Welfare of Japan, The number of vaccinated persons in routine vaccination (Japanese), https://www.mhlw.go.jp/topics/bcg/other/5.html. (Accessed 3 December 2020).

[55] H. Kamiya, Study on evidence and policy for improving usefulness of vaccines. MHLW grant study report. MHLW grants system #200940023B (in Japanese). http://mhlw-grants.niph.go.jp. (Accessed 1 December 2020).

[56] S. Iwata, N. Ishiwada, H. Sakata, T. Sakano, Y. Sato, T. Nakano, et al., Burden of illness of bacterial meningitis and bacteremia cause by Streptococcus pneumoniae in children (In Japanese), Jpn J Pediatr 61 (2008) 2206–2220.

[57] M. Shiragami, A. Mizukami, O. Leeuwenkamp, T. Mrkvan, E. Delgleize, Y. Kurono, et al., Cost-effectiveness evaluation of the 10-valent pneumococcal non-typeable Haemophilus influenzae protein D conjugate vaccine and 13-valent pneumococcal vaccine in Japanese children, Infect. Dis. Ther. 4 (2014) 93–112.

[58] A.G.S.C. Jansen, G.D. Rodenburg, S.C. Greef, E. Hak, R.H. Veenhoven, L. Spanjaard, et al., Invasive pneumococcal disease in The Netherlands: syndromes, outcome and potential vaccine benefits, Vaccine 27 (2009) 2394–2401.

[59] M.H. Rozenbaum, E.A. Sanders, A.J. van Hoek, A.G. Jansen, A. van der Ende, G. van den Dobbelsteen, et al., Cost effectiveness of pneumococcal vaccination among Dutch infants: economic analysis of the seven valent pneumococcal conjugated vaccine and forecast for the 10 valent and 13 valent vaccines, BMJ 340 (2010 Jun 2) c2509.

[60] Ministry of Health, Labour and Welfare of Japan, Health Japan 21 (the second term) analysis and assessment Project. https://www.mhlw.go.jp/stf/shingi2/0000196943.html. (Accessed 28 July 2020).

[61] M. Schad, J. John, Towards a social discount rate for the economic evaluation of health technologies in Germany: an exploratory analysis, Eur. J. Health Econ. 13 (2012 Apr) 127–144.

[62] T. Kitano, Dynamic transmission model of routine mumps vaccination in Japan, Epidemiol. Infect. 147 (2018) 1–8.

[63] A.E. Attema, W.B.F. Brouwer, K. Claxton, Discounting in economic evaluations, Pharmacoeconomics 36 (2018) 745–758.

[64] S.N. Ladhani, S. Collins, A. Djennad, C.L. Sheppard, R. Borrow, N.K. Fry, et al., Rapid increase in non-vaccine serotypes causing invasive pneumococcal disease in England and Wales, 2000-17: a prospective national observational cohort study, Lancet Infect. Dis. 18 (2018) 441–451.

[65] D.L.H. Koelman, M.C. Brouwer, D. van de Beek, Resurgence of pneumococcal meningitis in europe and Northern America, Clin. Microbiol. Infect. 26 (2020) 199–204.

[66] K. Huh, J. Jung, J. Hong, M. Kim, J.G. Ahn, J.H. Kim, et al., Impact of non-pharmaceutical interventions on the incidence of respiratory infections during the COVID-19 outbreak in Korea: a nationwide surveillance study, Clin. Infect. Dis. (2020) ciaa1682, https://doi.org/10.1093/cid/ciaa1682.

[67] Y.L. Hsu, H.C. Lin, H.M. Wei, H.C. Lai, K.P. Hwang, One benefit of COVID-19 measures in Taiwan: the reduction of influenza infections and severe complications, Influenza Other Respir Viruses 14 (2020) 757–758.

[68] T. Itaya, Y. Furuse, K. Jindai, Does COVID-19 infection impact on the trend of seasonal influenza infection? 11 countries and regions, from 2014 to 2020, Int. J. Infect. Dis. 97 (2020) 78–80.

[69] K.S. Chan, F.W. Liang, H.J. Tang, H.S. Toh, W.L. Yu, Collateral benefits on other respiratory infections during fighting COVID-19, Med. Clin. 155 (2020) 249–253.

[70] D.K. Yeoh, D.A. Foley, C.A. Minney-Smith, A.C. Martin, A.O. Mace, C.T. Sikazwe, et al., The impact of COVID-19 public health measures on detections of influenza and respiratory syncytial virus in children during the 2020 Australian winter, Clin. Infect. Dis. (2020 Sep 28) ciaa1475, https://doi.org/10.1093/cid/ciaa1475.