ORIGINAL ARTICLE

Comparison of Congenital Rubella Syndrome Cases at a Philippine Tertiary Hospital from 2009-2012 to 2019-2022

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ABSTRACT

Background and Objective. The Philippines does not have a national congenital rubella syndrome (CRS) surveillance or registry. Regular monitoring of CRS cases in hospitals, including in a Philippine tertiary hospital, helped in the past to provide clinico-epidemiologic data on CRS. This study aimed to continue providing clinico-epidemiologic data on CRS cases seen in the Philippine tertiary hospital from 2009-2012 and 2019-2022 and compare the cases seen from said timelines.

Methods. A cross-sectional study was used, employing chart review of patients newly diagnosed with CRS from 2009-2012 and 2019-2022 in the Department of Ophthalmology and Visual Sciences at the Philippine tertiary hospital.

Results. Forty-two patients newly diagnosed with CRS from 2009-2012 and 2019-2022 were included. Only 14 (33%) were serologically-confirmed cases (albeit qualitatively). Median age (first and third interquartile ranges) at consult was 1 year (0.4, 2.5). Twenty-four (57%) patients had maternal history of rashes and/or fever. Trimester of pregnancy when mother became symptomatic was not significantly correlated with chief complaint (p=0.20) and numbers of ophthalmic (p=0.68) and systemic manifestations (p=0.32). Cataract was the most common ophthalmic manifestation present in 40 (95%) patients. Twenty-six (62%) patients had other associated systemic findings of which hearing loss was the most common. Only 29 of 40 patients with cataract underwent lensectomy, with 23 patients having poor visual prognosis prior to surgery (5 with nystagmus alone, 10 with nystagmus and strabismus, and 8 with strabismus alone).

Discussion. Using ophthalmic manifestations as primary indicator, this study provided an update on the CRS cases in the country. Laboratory confirmation remains a challenge in diagnosing CRS as the tests are costly and not widely available. There was increase from 2009-2012 compared to 2019-2022 in number of patients who underwent surgical treatment for cataract but visual outcomes were suboptimal due to delay in consultation. Although there was a decrease in number of CRS cases seen in the Philippine tertiary hospital, this cannot be attributed to increased rubella-containing vaccine (RCV) coverage alone.

Conclusion. Provision of data from individual hospital-based studies similar to this highlights the need for a national CRS surveillance system or registry. This can better gauge the burden of CRS and identify the gap in RCV coverage.

Keywords: Congenital Rubella Syndrome, congenital cataract, pigmentary retinopathy, rubella-containing vaccine

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INTRODUCTION

Rubella infection during pregnancy can lead to congenital rubella syndrome (CRS) in up to 90% of neonates especially during the first trimester as a result of mother-to-fetus transmission of the virus.[1,2] Clinical manifestations of CRS include the triad of congenital abnormalities of the eyes, ears, and heart. In vaccinated but with low titers, or unvaccinated healthy individuals, a rubella infection can cause 3-day fever and rashes. However, its effects on a fetus can result in lifelong disabilities or death as well as high economic burden for the medical management and care.[3,4] CRS has no treatment except for the medical and surgical management of its individual clinical manifestations.[5] Rubella infection, however, is a vaccine-preventable disease.[1]

Rubella-containing vaccine (RCV) was already incorporated in the national routine immunization for Filipino children since 2009.[6] Yet, the reported incidence for CRS remained high after.[6,7] In 2017, a local multicenter study found 219 CRS in a span of six years. This was further reported as possible underestimations since the country does not have active surveillance for CRS.[7] Despite national efforts to increase RCV coverage, the high number can be due to a significant proportion of women of reproductive age susceptible to rubella infection due to either not receiving RCV at all or having low immunoglobulin titers despite receiving RCV. The RCV program in the country does not extend coverage to women of childbearing age.

The World Health Organization (WHO) recommends such a program to address the burden of CRS by ensuring that women of childbearing age are protected by the RCV from rubella.[7] The country also does not recommend routine rubella susceptibility screening for women of childbearing age.[7] The absence of both highlights the need for at least a dedicated CRS surveillance or registry to keep track of the disease. The Department of Health (DOH) only maintains a combined measles and rubella infection surveillance program.[8] Regular monitoring of CRS cases in hospitals, including in a Philippine tertiary hospital, has helped in past surveillance and can continue to provide the needed local data on CRS.[6,7] And since 2014, there has been no update on CRS. As such, this study aimed to provide clinico-epidemiologic data on CRS cases seen in a Philippine tertiary hospital from 2009-2012 and 2019-2022 and compare the cases seen from both timelines.

METHODS

This cross-sectional study was conducted with ethics approval from the University of the Philippines Manila Research Ethics Board and followed the principles of the Declaration of Helsinki. Data handling of the patients adhered to the Data Privacy Law of 2012. This study employed a chart review of patients of the Division of Pediatric Ophthalmology and Strabismus of the Department of Ophthalmology and Visual Sciences of the Philippine General Hospital diagnosed from 2019 to 2022 with Congenital Rubella Syndrome (CRS) based on the WHO classification. Also included were diagnosed patients with CRS seen in the Division from 2009 to 2012, the only timeline with available complete clinical and surgical census, for comparison. Patients seen from the two timelines whose charts met the case definition of CRS and with pertinent data needed in the study were included. CRS is defined and classified based on the criteria approved by the Council of State and Territorial Epidemiologists published in 2009 and used by the WHO in its reports and proceedings.[1] Cases are either *suspected, probable, confirmed,* or *infected only* (Table 1).

Patients with congenital cataract or retinopathy from other causes such as trauma were excluded. Data on age at onset of symptoms, age at the first consult, chief complaint, maternal history of infection, and maternal and infant vaccination records, if present, were collected. Ocular and systemic findings were tabulated. Visual prognosis was considered poor if the patient also has nystagmus or/and strabismus prior to surgery. Ophthalmic surgeries performed were also noted along with the visual acuity after said procedures, if available.

Frequency distribution, percentages, and central tendencies were used to summarize data. Descriptive and statistical comparisons including Student's t-test to compare the ages of the CRS patients seen from the two timelines were done. Correlation using the Spearman rank correlation test was done between the trimester of pregnancy where the mother became symptomatic to the number of ophthalmic and systemic manifestations that patients had. A p-value of less than 0.05 was considered statistically significant.

RESULTS

A total of 42 patients newly diagnosed with CRS from 2009-2012 and from 2019-2022 seen in the Division of the Pediatric Ophthalmology and Strabismus were included in the study. Only 14 (33%) were confirmed cases. The confirmed cases were found reactive to rubella immunoglobulin G (IgG) using the Toxoplasma, Rubella, Cytomegalovirus and Herpes (TORCH) test. Two patients were also reactive to cytomegalovirus IgG while one was also reactive to Herpes IgG. An average of 5.25 patients were seen annually from the two timelines. There were no new CRS patients seen in 2020 and 2022.

Twenty-three (55%) patients were male. The median age (first and third interquartile ranges) at initial consult was 1 (0.4,2.5) year. Only 24 (57%) patients had maternal history of rashes and/or fever. Mothers of 17 patients became symptomatic in the 1st trimester of pregnancy, four during 2nd trimester, two during 3rd trimester and one with no additional data. There were no significant correlations between the trimester of pregnancy when the mother became symptomatic to the infant's chief complaint (r= -0.28,

Table 1. Classification of Congenital Rubella Syndrome (CRS) *Adopted from Lanzieri et al., 2020*[1]

Suspected: An infant who does not meet the criteria for a probable or confirmed case but who has one or more of the following findings:
- cataracts,
- congenital glaucoma,
- congenital heart disease (most commonly patent ductus arteriosus or peripheral pulmonary artery stenosis),
- hearing impairment,
- pigmentary retinopathy,
- purpura,
- hepatosplenomegaly,
- jaundice,
- microcephaly,
- developmental delay,
- meningoencephalitis, or
- radiolucent bone disease.

Probable: An infant who does not have laboratory confirmation of rubella infection but has at least two of the following, without a more plausible etiology:
- cataracts or congenital glaucoma,
- congenital heart disease (most commonly patent ductus arteriosus or peripheral pulmonary artery stenosis),
- hearing impairment, or
- pigmentary retinopathy;

OR

An infant who does not have laboratory confirmation of rubella infection but has at least one or more of the following, without a more plausible etiology:
- cataracts or congenital glaucoma,
- congenital heart disease (most commonly patent ductus arteriosus or peripheral pulmonary artery stenosis),
- hearing impairment, or
- pigmentary retinopathy;

AND

One or more of the following:
- purpura,
- hepatosplenomegaly,
- microcephaly,
- developmental delay,
- meningoencephalitis, or
- radiolucent bone disease.

Confirmed: An infant with at least one of the symptoms clinically consistent with congenital rubella syndrome listed above; and laboratory evidence of congenital rubella infection demonstrated by:
- isolation of rubella virus, or
- detection of rubella-specific immunoglobulin M (IgM) antibody, or
- infant rubella antibody level that persists at a higher level and for a longer period of time than expected from passive transfer of maternal antibody (i.e., rubella titer that does not drop at the expected rate of a two-fold decline per month), or
- a specimen that is PCR-positive for rubella virus.

Infection only: An infant without any clinical symptoms or signs of rubella but with laboratory evidence of infection demonstrated by:
- isolation of rubella virus, or
- detection of rubella-specific immunoglobulin M (IgM) antibody, or
- infant rubella antibody level that persists at a higher level and for a longer period of time than expected from passive transfer of maternal antibody (i.e., rubella titer that does not drop at the expected rate of a two-fold decline per month), or
- a specimen that is PCR-positive for rubella virus.

p=0.20), infant's number of ophthalmic findings (r= -0.09, p=0.68), and infant's number of systemic findings (r= -0.21, p=0.32).

All patients presented with ophthalmic findings. Only five patients had isolated ophthalmic manifestation: four with cataracts and one with pigmentary retinopathy. Cataract was the most common ophthalmic manifestation seen in 40 patients with 23 having bilateral involvement. The distribution of ophthalmic findings is listed in Table 2.

Twenty-six patients (62%) had associated systemic findings. Seventeen patients had more than one non-ophthalmic systemic manifestations. Hearing loss was the most common in 16 (34%) patients. Table 3 summarizes the distribution of non-ophthalmic systemic manifestations. Not included in the table were manifestations only seen in one patient: oligohydramnios, prematurity, hydrocephalus, jaundice, attention deficit hyperactive disorder, epilepsy, cerebral palsy, flat nasal bridge, down slanting of palpebra, and stunting.

Of the 40 patients with cataract, only 29 (72%) underwent lensectomy with primary posterior capsulotomy, anterior vitrectomy, and secondary intraocular lens placement. Twenty-three patients already have preoperative signs of poor visual prognosis: five with nystagmus alone, 10 with nystagmus and strabismus, and eight with strabismus alone).

Fifteen patients newly diagnosed with CRS were seen from 2019 to 2022. Eight (53%) were confirmed cases,

Table 2. Distribution of Ophthalmic Findings

Ophthalmic Finding	Number of patients	Percentage
Cataract	40	85
Unilateral	17	
Bilateral	23	
Pigmentary retinopathy	22	47
Strabismus	24	51
Exotropia	13	
Esotropia	11	
Microcornea	6	13
Optic nerve findings	2	4
Iris pathology	1	2
Phthisis	1	2
Corneal scar	1	2

** Some patients presented with multiple ophthalmic symptoms (e.g., a patient with cataract, retinopathy, and strabismus)*

Table 3. Distribution of Systemic Findings

Systemic finding	Number of patients	Percentage
Hearing loss	16	34
Developmental delay	12	26
Congenital heart disease	10	21
Microcephaly	4	8
Autism	2	4
Palate abnormalities	2	4

five (33%) probable, and two (14%) suspect. There were eight (53%) male patients. The median age (first and third interquartile range) at initial consult was 0.7 (0.3,1.5) year. Eight (53%) patients had maternal history of rashes and/or fever, all reported during the 1st trimester. All 15 patients presented with ophthalmic findings. Only one (7%) patient had an isolated ophthalmic finding. Cataract was the most common ophthalmic finding present in 14 patients, 11 (78%) with bilateral involvement. Twelve (80%) patients underwent lensectomy with primary posterior capsulotomy, anterior vitrectomy without intraocular lens placement. Seven (47%) patients already have nystagmus prior to surgery. Hearing loss was the most common associated systemic finding present in nine (60%) patients (Table 4).

For comparison, 27 patients were newly diagnosed with CRS from 2009 to 2012. Six (22%) were confirmed cases, 15 (56%) probable, and 6 (22%) suspect. The proportion of confirmed cases was lower than those seen from 2019 to 2022. Fifteen (56%) patients were male. The median age at consult was 1.5 (0.4,2.9) years, which was not significantly different than of the patients seen in 2019-2022 (p=0.98) (Table 4). Sixteen (59%) patients had maternal history of rashes and/or fever. The mothers of the nine patients became symptomatic in the 1st trimester of pregnancy, four in 2nd trimester, and two in the 3rd trimester. One did not have additional data. Twenty-six patients presented with ophthalmic findings. Four (15%) patients had an isolated ophthalmic manifestation: three with cataract and one with pigmentary retinopathy. This was more than those seen from 2019-2022. Cataract remained the most common ophthalmic finding present in 26 patients. Twelve (46%) had bilateral involvement, lower than in patients seen from 2019-2022. Seventeen (63%) underwent lensectomy with primary posterior capsulotomy, anterior vitrectomy without intraocular lens placement. Nine (35%) patients had nystagmus, lower than in patients seen from 2019-2022. Hearing loss and developmental delay were the most common associated systemic findings present in seven patients each (Table 4).

Table 4. Comparison of CRS Cases Seen from 2009-2012 to 2019-2022

	2009-2012	2019-2022	*p*-value
Number of Patients seen	27	15	
Confirmed	6	8	
Probable	15	5	
Suspect	6	2	
Male	15 (56%)	8 (53%)	
Age	1.5 years	0.7 year	0.98
Maternal history of rashes and/or fever	16 (59%)	8 (53%)	
With ophthalmic findings	26 (96%)	15 (100%)	
With systemic findings	14 (52%)	13 (87%)	
Underwent surgery	17 (63%)	12 (80%)	

DISCUSSION

Using ophthalmic manifestations as primary indicator, this study provided an update on the CRS cases in the country. These data are significantly needed considering the absence of a national CRS surveillance. This is similar to most local CRS data which came from studies and literature done in individual hospitals and published by independent groups. In 2017, Lopez et al. did a cross-sectional study in four tertiary government hospitals namely Philippine General Hospital in Manila, Philippine Children's Medical Center in Quezon City, Vicente Sotto Memorial Medical Center in Cebu City, and Southern Philippines Medical Center in Davao City, to get an estimate of the national CRS burden where it found similar age at diagnosis and male predominance.[6] Similarly, rubella infections in children and adults do not have an independent surveillance system and are just being monitored only as a part of the measles surveillance.[8] Rubella cases that did not need hospital admission go unreported. Hospitalization is not common since the infection lasts only for three days and does not often have systemic complications like rubeola.[9] Similarly, up to half of those with rubella infection are asymptomatic. As such, the national burden of both CRS and rubella infections remains underreported making it hard to evaluate the effectiveness of national programs on the use of rubella-containing vaccines.

Aside from the absence of a dedicated CRS surveillance, other challenges in estimating the national burden of CRS are the accessibility and affordability of laboratory confirmation. Despite the devastating medical seriousness of CRS complications, the public health consequences and the accompanying financial burden of its management, immunologic screening is still not included in Newborn Screening and Expanded Newborn Screening Programs in the country.[1,4,9-11] These challenges are common among developing countries as the tests are costly and not widely available.[11] The tests just for Rubella IgG and IgM are already worth P3,500 in the Philippine tertiary hospital.[4] It costs more if the complete TORCH panel is requested which can be helpful. Coinfection occurs which can complicate management or may lead to clinical misdiagnosis.[12,13] The tests are also not readily available even in major cities.[6] This makes diagnosing CRS in the country mostly clinical, as evidenced by the low number of laboratory-confirmed cases in this study and Lopez et al.'s as well.[6] The presence of maternal history of fever and rashes remains helpful in clinically diagnosing CRS. However, its absence should not prevent us from considering CRS since only around 60% of our patients presented with maternal history of fever and rashes. This finding was similar to a study in Vietnam.[14]

Although cataract is treatable, our patients sought eyecare relatively late based on their median age at initial consult even when compared to series conducted in other countries. This significantly affected their visual outcomes as deprivation amblyopia from the cataract can set in as early as 6-8 weeks

especially for unilateral cases.[15] It is then recommended that public awareness on the treatability of congenital cataract be increased. The public should also be made aware on the need for early intervention as there was no significant difference between the age at consultation of patients seen from 2009-2012 to those seen in 2019-2022. Similarly, accessible and affordable eye care services should be increased as only 72% of the cases underwent surgery.[16] Although there was an increase in patients who underwent surgery in 2019-2022 compared to those seen from 2009-2012, the effect on the visual outcomes was hard to quantify. Patients had short follow-up periods and precluded objective measurements of visual acuity. This is further complicated by the presence of developmental delays and autism in some patients. However, the high proportion of nystagmus among our patients due to the late age at initial consultation is indicative of poor visual prognosis. Shah et al. highlighted the importance of early surgical intervention for good visual outcomes in CRS.[15] Although one year is already a significant improvement from the mean age of 24 months in the congenital cataract series of Tecson and Santiago in the same institution from 2000-2003, further improvement in terms of early diagnosis and eventual surgical intervention can still be achieved due to the easy discernability of cataract.[17]

All patients manifested with ophthalmic abnormalities, with cataract as the most common.[1,6] This, however, is probably reflective of selection biases as the study was conducted in an Ophthalmology department. Hearing loss was the most common non-ophthalmic systemic finding in this study, different from Lopez et al. and series in other countries which listed heart abnormalities.[6] Unlike other literature also, this study found that the onset of maternal CRS symptoms was unrelated to the chief complaint and number of ophthalmic and systemic findings.[18] Maternal rubella infection in early pregnancy or periconception period has a risk of developing CRS in 90% of the cases with more severe number of ophthalmic and systemic manifestations.[18] On the other hand, when acquired beyond 18 weeks of gestation, the fetus might be infected but does not typically develop signs and symptoms of CRS.[18] The result may be due to inaccuracies in recall of the timing of the infection in pregnancy as most presented with mild symptoms.

Less patients with CRS were seen from 2019-2022 compared to those from 2009-2012. An average of seven new CRS patients were seen from 2009-2012, higher than the four seen from 2019-2022. This decrease may not be attributable to increased vaccine coverage but perchance to the COVID-19 pandemic. There was no CRS case seen in 2020, when the Philippine tertiary hospital limited its operations to COVID-19 cases, and in 2022. The increased percentage of confirmed cases from 2019-2022 compared to 2009-2012 can be a result of the recent Division protocol to request TORCH titer test for patients suspected with CRS.

The persistence of CRS cases in the Philippine tertiary hospital despite the integration of RCV in the national immunization programs for children echoes the need to extend its coverage to women of reproductive age.[11] This may be cheaper than recommending TORCH screening prior to planning to get pregnant.[11] Similarly, the dependence to individual hospitals to report on CRS cases in the country highlights the need for a national surveillance for rubella, independent of measles and for CRS. This is to better gauge the national burden of both diseases and evaluate the gap in RCV coverage, especially considering the effects of the then Sanofi Pasteur's Dengvaxia issue and the ongoing COVID-19 pandemic.[19,20]

CONCLUSION

Provision of data from individual hospital-based studies similar to this highlights the need for a national CRS surveillance system which can better gauge the burden of CRS and identify the gaps in RCV coverage. Although there was a decrease in number of CRS cases seen in the Philippine tertiary hospital, this cannot be attributed to increased RCV coverage alone. There was increase in number of patients who underwent surgical treatment for cataract but visual outcomes were poor due to delay in consultation.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

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REFERENCES

1. Lanzieri T, Redd S, Abernathy E, Icenogle J, Congenital Rubella Syndrome - Vaccine Preventable Diseases Surveillance Manual | CDC [Internet]. 2020 [cited 2023 Jan]. Available from: https://www.cdc.gov/vaccines/pubs/surv-manual/chpt15-crs.html
2. Mendez CLM, Rubella [Internet]. 2021 [cited 2023 Jan]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK559040/#_NBK559040_pubdet_
3. Toizumi M, Vo HM, Dang DA, Moriuchi H, Yoshida LM. Clinical manifestations of congenital rubella syndrome: A review of our experience in Vietnam. Vaccine. 2019 Jan;37(1):202-9. doi: 10.1016/j.vaccine.2018.11.046.
4. Tan RJD, Leon LP. The cost of managing congenital rubella syndrome in a tertiary government hospital in Northern Luzon, Philippines. Acta Med Philipp. 2023;57(1):41-6. doi:10.47895/amp.vi0.4066
5. Shukla S, Maraqa NF, Congenital Rubella. In: StatPearls [Internet]. 2022 [cited 2023 Jan]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK507879/
6. Lopez AL, Raguindin PF, Del Rosario JJ, Najarro RV, Du E, Aldaba J, et al. The burden of congenital rubella syndrome in the Philippines: results from a retrospective assessment. Western Pac Surveill Response J. 2017 Jun;8(2):17-24. doi: 10.5365/wpsar.2017.8.1.006.
7. Lopez AL, Raguindin PFN, Silvestre MA, Fabay XCJ, Vinarao AB, Manalastas R. Rubella and congenital rubella syndrome in the

Philippines: a systematic review. Int J Pediatr. 2016;2016:8158712. doi: 10.1155/2016/8158712.
8. Department of Health, Epidemic-prone Disease Case Surveillance (EDCS) Morbidity Week No. 18. 2022 [cited 2023 Jan]. Available from: https://doh.gov.ph/sites/default/files/statistics/2022%20EDCS%20Weekly%20Surveillance%20Report%20No.%2018.pdf
9. Winter AK, Moss WJ. Rubella. Lancet. 2022 Apr;399(10332): 1336-46. doi: 10.1016/S0140-6736(21)02691-X.
10. Newborn Screening Resource Center (NRSC), Newborn Screening Manual of Operations [Internet]. 2019 [cited 2023 Jan]. Available from: https://doh.gov.ph/sites/default/files/health_programs/Newborn%20Screening%20Manual%20of%20Operations%20v2019.pdf
11. Kaushik A, Verma S, Kumar P. Congenital rubella syndrome: A brief review of public health perspectives. Indian J Public Health. 2018 Jan-Mar;62(1):52-4. doi: 10.4103/ijph.IJPH_275_16.
12. Tan RJD, Santiago DE, Alhasan YE. A clinically diagnosed congenital rubella syndrome and congenital cytomegalovirus co-infection. Acta Med Philipp. 2022;56(12):58-64. doi:10.47895/amp.vi0.3310
13. Tan RJD. Congenital cytomegalovirus infection initially managed as congenital rubella syndrome. Acta Med Philipp. 2022;56(13): 81-4. doi:10.47895/amp.vi0.3694
14. Toda K, Reef S, Tsuruoka M, Iijima M, Dang TH, Duong TH, et al. Congenital rubella syndrome (CRS) in Vietnam 2011-2012--CRS epidemic after rubella epidemic in 2010-2011. Vaccine. 2015 Jul;33(31):3673-7. doi: 10.1016/j.vaccine.2015.06.035.
15. Shah SK, Praveen MR, Vasavada AR, Vasavada VA, Carelli R, Trivedi RH, et al. Long-term longitudinal assessment of postoperative outcomes after congenital cataract surgery in children with congenital rubella syndrome. J Cataract Refract Surg. 2014 Dec;40(12):2091-8. doi: 10.1016/j.jcrs.2014.04.028.
16. Tan RJD, Dacuma MGB. Factors affecting childhood blindness and visual impairment in Baguio General Hospital and Medical Center. Phil J Health Res Dev. 2021 Jul-Sep;25(3):54-63.
17. Tecson JV, Santiago APD. Profile of childhood cataract cases at the Philippine General Hospital. Philipp J Ophthalmol. 2004 Jul-Sep;29(3):140-3.
18. Center for Disease Control and Prevention, 5.1 Congenital Rubella Syndrome (CRS) [Internet]. 2022 [cited 2023 Jan]. Available from: https://www.cdc.gov/ncbddd/birthdefects/surveillancemanual/chapters/chapter-5/chapter5-1.html#:~:text=If%20maternal%20rubella%20infection%20is,rubella%20infection%20(CRI)%20only.
19. Larson HJ, Hartigan-Go K, de Figueiredo A. Vaccine confidence plummets in the Philippines following dengue vaccine scare: why it matters to pandemic preparedness. Hum Vaccin Immunother. 2019; 15(3):625-7. doi: 10.1080/21645515.2018.1522468.
20. Zhong Y, Clapham HE, Aishworiya R, Chua YX, Mathews J, Ong M, et al. Childhood vaccinations: Hidden impact of COVID-19 on children in Singapore. Vaccine. 2021 Jan;39(5):780-5. doi: 10.1016/j.vaccine.2020.12.054.