

TO STUDY THE IMMUNE RESPONSE TO MR VACCINE IN CHILDREN

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Abstract

Background: India, along with other WHO-SEAR countries, in September 2013, had resolved to eliminate measles and control rubella/congenital rubella syndrome (CRS) by 2020. In that direction, Ministry of Health & Family Welfare had introduced Rubella and Measles vaccine in its Universal Immunization Programme (UIP) as Measles-Rubella (MR) vaccine. As a part of a measles and rubella (MR) campaign, the MR vaccine replaced the two-dose measles vaccine at 9–12 months and 16–24 months of age under the Universal Immunization Program (UIP). **Aim of the study 1)** To assess immunogenicity of MR vaccine in children and make a comparative study between those who were vaccinated with MMR vaccine and those not vaccinated before with MMR. 2) To detect the antibody titre of Rubella and Measles in children vaccinated only with MR vaccine. **Materials and Methods:** This was a prospective study of one year duration. Children aged 2-15 years attending the paediatrics OPD at Government medical college Kozhikode were enrolled for the study. Children with history of exanthematous fever in the past were excluded. Study participants were classified broadly into 2 groups. Those who were immunised with MR vaccine and those who were not immunised with MR vaccine. Those who had taken MR vaccine, were further categorized into those vaccinated with and without MMR at 15 months. IgG antibodies were measured by enzyme linked immunoassay (ELISA) in serum samples 3- 11 months after vaccination. A child was considered seropositive if antibody levels were higher than the assay cut-off level set by the ELISA kit. **Result:** As measured by the Enzywell, ELISA IgG Quantitative estimation kit, the serum Rubella IgG level was higher than the assay cut-off in 97.5% of samples and 84.1% were seropositive for Measles using CALBIOTECH (California), IgG quantitative ELISA kit for those vaccinated with MR vaccine. The study shows that 26.4% of unimmunised children are protected against Rubella. This may be attributed to their natural immunity. 73.6% of unimmunised children are not protected against Rubella. **Conclusion:** In conclusion our study finding suggest that it is strongly recommended for children to take these vaccines, and, if parents are panicking too much, the schools should arrange for paediatricians to come and address their issues. This additional MR vaccine gives 100% immunity against the disease. It not only ensures immunity to those vaccinated but also prevent its spread.

INTRODUCTION

Rubella (German measles) is an acute exanthematous viral infection of children and adults caused by the rubella virus. Rubella is an RNA virus, a member of the Togaviridae family and the genus Rubivirus. The clinical illness, is acute, mild and self-limiting, characterized by rash, fever, and lymphadenopathy and resembles a mild case of measles (rubeola).^[1] It affects both children and

adults with the vast majority of cases occurring in children less than 15 years of age.

Rubella infection can spread from a pregnant woman to unborn child or through secretion from another infected person. Rubella infection occurring during early pregnancy or immediately before conception may result in congenital rubella syndrome (CRS), miscarriage or fetal death.^[2] CRS often results in multiple birth defects including heart problems, deafness and blindness. More than 100,000 children are born with CRS each year. The lifelong complications and disabilities can have an

immeasurable emotional, social and financial cost for families. Measles is a highly contagious viral disease that is often deadly. Measles is one of the world's most contagious diseases. Complications including otitis media, laryngotracheobronchitis, diarrhea and pneumonia, occur in approximately 30% of reported cases of measles. The risk for severe complications or death from measles increases for children less than five years of age, malnourished children, immune compromised children, and those living in crowded conditions.^[3] Measles and rubella are “vaccine-preventable diseases” (VPD). The WHO recommends that in order to eliminate congenital rubella syndrome and to prevent the complications associated with measles, countries should use the measles, mumps and rubella (MMR) vaccine in a two-dose schedule for routine childhood immunization programs.^[4,5] Rubella can be prevented with MMR vaccine. MMR protects against three diseases: measles, mumps, and rubella. CDC recommends that children should get two doses of MMR vaccine, starting with the first dose at 12 through 15 months of age, and the second dose at 4 through 6 years of age.^[6] MMR vaccine is very safe and effective. One dose of the MMR vaccine is about 97% effective at preventing rubella.^[7] In the pre-vaccination era, more than 90% of children in the world under the age of 15 years were infected with measles virus, resulting in more than 2 million deaths annually. With the introduction of active immunization, the global number of measles cases decreased significantly. During 2000–2011 period, annual measles incidence decreased by 65% worldwide, and the estimated number of measles deaths decreased by 71%.^[8] The European Vaccination Action Plan for 2015-2020, based on the World Health Organization (WHO) Global Vaccination Action Plan, anticipated the elimination of measles in the WHO European Region.^[9] According to this Plan, the interruption of indigenous measles transmission should have been achieved by 2015 and elimination in the WHO European Region should have been declared in 2018.^[10]

The prerequisites for the eradication of measles have been met already because,

- Humans are the only natural reservoir of MV,
- There is no long-term carriage and shedding of Measles Virus
- There is no antigenic diversity among strains and genotypes, so the available vaccines provide protection against all circulating strains of MV,
- The low price of vaccine allows it to be universally available, and
- The vaccine provides long-term protection in a high percentage of vaccinated persons.^[10]

However, continuous transmission with occasional measles outbreaks in the European region still occurs.^[10]

The elimination goals have been unmet not because of the suboptimal characteristics of the available vaccines or disease features, but because of the

“logistical” failure of the health systems to achieve optimal vaccination coverage in the European population for a long period. The reason could be immunization coverage gaps due to migration of population, difficulties in vaccine supply, unequitable access to vaccine of particular population subgroups, and breaches in the cold chain affecting vaccine quality, lack of awareness of the need for vaccination, fear of adverse events, which results in delayed or missed vaccinations, or refusal of vaccination by anti-science vaccine opponents.^[11] In 2019, the United States reported the highest number of measles cases and outbreaks since measles was eliminated in 2000. COVID-19 pandemic drastically reduced opportunities for travelers infected with measles.^[12] Rubella was declared eliminated from the United States in 2004. Rubella incidence in the United States has decreased by more than 99% from the pre-vaccine era.^[13] In India, Measles vaccine was included in the Universal Immunization Programme in 1990.^[14] First and second doses of measles vaccines were introduced in the Universal Immunization Program (UIP) in 1985 and 2010, respectively.^[14,15]

IAP recommends administration of one dose of MMR vaccine at 12-15 months of age preceded by one dose of Measles vaccine at 9+ months ;and has also stated the need for a second dose of MMR as one single dose of MMR does not offer sufficient protection.^[16] As per the Health Management Information System (HMIS), and as per National Family Health Survey-4 (NFHS-4 survey, 2015–16), the countrywide coverage of measles containing vaccine 1, at age 12–23 months stands at 90% and 81.1% respectively.^[17] According to WHO and UNICEF 2018 data, MCV1 and MCV2 have an estimated coverage of 90% and 80%, respectively.^[18] Following the South East Asia regional committee resolution in September 2013, India had set a goal for measles elimination and rubella/CRS control by 2020.^[19] To achieve this goal, the National Technical Advisory Group of Immunisation (NTAGI), in June 2014, recommended the introduction of the measles–rubella (MR) vaccine in routine immunization programs following a nationwide MR campaign to increase population immunity against measles and rubella. Before the MR campaign, measles-only vaccine was being given at 9 months of age under the UIP in all the states, while MMR vaccine was being given at 15 months of age in a few states under the UIP.^[20]

The aim of the country-wide MR vaccine campaign was to reach 95% of children with the second dose, individually completing their inoculation, and, at the population-level, ‘eradicating’ the disease from India.

Why the need for MR vaccine?

The MR (and MMR) vaccine when given as single primary dose, works for 9 out of 10 children. 1 in 10 children do not acquire full immunity from a single dose, and thus are still susceptible to measles and

rubella unless they get a second dose. Because of that, while the country wide coverage of the primary MR(or MMR) dose stands at a (relatively) respectable 83 to 90% of children, actual immunity falls far short. Hence a second dose is necessary for all children. It strengthens immunity for those already covered by the initial primary dose, and the re-exposure to the viruses establishes lasting immunity for those who didn't get it from the single dose. Combined, the MR (or MMR) vaccine doses ensure lifetime immunity to two serious diseases. Boys and men too cannot be excluded from rubella immunization because they can transmit rubella to pregnant women. The private sector generally vaccinates in accordance with the Indian Academy of Paediatrics (IAP) schedule, which recommend 3 doses of MMR for routine vaccination at 9, 15, and 60 months, respectively.^[21] Under the national immunization programme, two doses of measles vaccines provided at 9–12 months and 16–24 months under the UIP have been replaced by the MR vaccine after the MR campaign in a phased manner. It is the only effective way to prevent these infections. Live, or attenuated, vaccines are avoided in anyone with a compromised immune system.^[22] The MR vaccine used in the immunization program is a live-attenuated vaccine: containing the Edmonston strain of measles and the RA 27/3 strain of rubella and protects against two diseases measles and rubella. The same components are part of MMR vaccine used in state immunization programmes in India and in the private sector for immunization at 9 months, 15 months, and 5 years and is by the same manufacturer. The MR vaccine used in India is WHO prequalified. Most of the currently licensed vaccines are based on the live, attenuated RA 27 / 3 strain of rubella virus propagated in human diploid cells. Other attenuated rubella vaccine strains include the Matsuba, DCRB19, Takahashi, Matsuura and TO-336 strains used primarily in Japan, and the BRD-2 strain used primarily in China. Vaccination results in high (>95%) seroconversion rates and protection is generally assumed to be lifelong, although rubella antibodies may fall below detectable levels. In campaigns, all children in the target age group are vaccinated irrespective of previous immunization status. The Measles-Rubella campaign is one of the massive public health undertakings targeting nearly 41 crore children across the country over a period of two to three years. The vaccination was provided through sites at schools and outreach session sites. This will be a major step towards reducing measles mortality burden in the country and reducing disabilities among children due to (CRS) congenital rubella syndrome.^[23]

MATERIALS AND METHODS

This prospective study was carried out at Government medical College Kozhikode, a tertiary

care hospital in Kerala, South India over a period of one year (Dec 2017-Nov 2018). The institutional review board clearance was obtained prior to commencement of the study. Samples were collected from children between the age group of 2 to 15 years attending the pediatrics OPD. Their immunization status was noted from their routine immunization cards and data collected from parents. Those with recorded history of measles/rubella or any history of exanthematous fever were excluded from the study to rule out natural immune response to rubella and measles.

3-5ml venous blood samples were collected from these children in sterile tubes; serum separated by centrifuging the clotted samples and stored at -20°C till antibody level estimation was done.

The antibody levels against Rubella were estimated using the Enzywell, DIESSE (Italy) ELISA IgG Quantitative estimation kit. According to the manufacturer, antibody level <7 IU/ml was considered as non-immune, between 7-13 IU/ml as doubtful and > 13 IU/ml as immune or protective for Rubella. Antibody levels for Measles was analysed using CALBIOTECH (California), IgG quantitative ELISA kit. Values <0.9U/ml were considered as negative, 0.9 to 1.1 U/ml as borderline positive and >1.1U/ml as positive for Measles according to the manufacturer.

Statistical analysis

The children were broadly categorized into two categories for comparison. Those who had taken MR vaccination and those who had not taken MR vaccination. Those who had received MR vaccination were further classified into those who had received MR alone and those who had received both MR and MMR (as per immunization schedule at 15 months). Those who had NOT taken MR were further classified into those who had received only MMR vaccine and those who were unimmunized for any measles or rubella vaccine. Thus we had 4 categories Group A, B, C and D.

Group A: Children who are immunized with MR vaccine only.

Group B: Children who are immunized with both MR and MMR vaccine.

Group C: Children who are immunized with MMR vaccine only.

Group D: Children NOT immunized with MR or MMR vaccine

Seroprotection: The children having antibody levels above the assay cut-off, as specified by the ELISA kits were considered as seroprotected. Those with Equivocal antibody titres were included among seroprotected group.

RESULTS

We included 214 children in the age group of 2 and 14 years (mean = 6.83±3.16) in the study, of which 137 were boys and 77 were girls. All 214 samples were checked for rubella and measles antibodies.

158 children had been vaccinated with MR vaccine as part of the MR vaccination campaign. Out of these 158 children, 94 children had been vaccinated with only MR vaccine and 64 children had been vaccinated with both MMR and MR vaccine. 22 children had received only MMR vaccination and 34 children didn't receive any vaccine. The time interval between vaccination and antibody titre assay ranged from 12 weeks to 44weeks. As measured by the Enzywell, ELISA IgG Quantitative estimation kit, the Rubella serum IgG level was higher than the assay cut-off in 97.5% of samples and 84.1% were seropositive for Measles using CALBIOTECH (California), IgG quantitative ELISA kit for those vaccinated with MR vaccine. No significant relationship was found between seropositivity and age or gender. In our study the

majority had received MR vaccine between 5 to 10years of age. The duration since receiving MR vaccine at the time of enrolment varied from 5months to 15 months.

The degree of immunity against Rubella is interpreted as follows:(IMMUNE: when the IgG concentration of the sample is >13IU/mL

Non-Immune: if the concentration is < 7 IU/mL

Doubtful:if the concentration ranges between 7 and 13 IU/mL.

The degree of immunity against Measles is interpreted as follows:(IMMUNE: when the IgG concentration of the sample is >1.1IU/mL.**Non-immune:** if the concentration is < 0.9 IU/mL

Borderline Positive: If the concentration ranges between 0.9- 1.1 IU/mL

Group A:MR only Results

Table 1: Basic parameter of the participants in group A : Only MR N=94

sex	Frequency	Percent
Male	66	70.2
Female	28	29.8
Age		
<5 years	16	17.0
5-10years	51	54.3
11-15years	27	28.7
Fever with rash		
Yes	2	2.1
No	92	97.9
Measles vaccine		
Yes	93	98.9
No	1	1.1
Other vaccines		
Fully immunised	83	88.3
Partially immunised	10	10.6
Non responders	1	1.1
H/O Chronic illness		
Yes	6	6.4
No	88	93.6

Table 2: Rubella titre

	Frequency	Percent
Non immunised	1	1.1
Doubtful	1	1.1
Immunised	92	97.9
Total	94	100.0

Table 3: Measles titre

	Frequency	Percent
Negative	12	12.8
Borderline	14	14.9
Positive	68	72.3
Total	94	100.0

Group B- MR+MMR

Table 4: Basic parameter of the participants in group B :N= 64

	Frequency	Percent
Male	34	53.1
Female	30	46.9
Age		
Less than 5 yrs	46	71.9
5-10yrs	17	26.6
More than 10yrs	1	1.6
Fever with rash		
Yes	4	6.3
No	60	93.8

Measles vaccine		
Yes	64	100.0
Other vaccines		
Fully immunised	60	93.8
Partially immunised	2	3.1
Non reactors	2	3.1
H/O Chronic Illness		
Yes	6	9.4
No	58	90.6

Table 5: Rubella Titre

	Frequency	Percent
Non immunized(<7)	3	4.7
Immunized(>13)	61	95.3
Total	64	100.0

Table 6: Measles Titre

	Frequency	Percent
Negative(<0.9)	13	20.3
Borderline(0.9-1.1)	9	14.1
Positive (>1.1)	42	65.6
Total	64	100.0

Group C: MMR only

Table 7: Basic parameter of the participants in group C; N= 22

	Frequency	Percent
Sex		
Male	13	59.1
Female	9	40.9
Age		
Less than 5 years	8	36.4
5 - 10 years	14	63.6
Fever with rash		
Yes	1	4.5
No	21	95.5
H/O chronic illness		
Yes	5	22.7
No	17	77.3
Measles Vaccination		
Yes	22	100.0
Other vaccines		
Fully immunised	19	86.4
Partially immunised	3	13.6

Table 8: Rubella Titre

	Frequency	Percent
Rubella		
Less than 7	3	13.6
7 -13	1	4.5
More than 13	18	81.8
Total	22	100.0

Table 9: MesalesTitre

	Frequency	Percent
Measles		
Less than 0.9	3	13.6
0.9 - 1.1	6	27.3
More than 1.1	13	59.1
Total	22	100.0

Group D- Unimmunized

Table 10: Basic parameter of the participants in group D; N=34

	Frequency	Percent
Sex		
Male	24	70.6
Female	10	29.4
Age		
Less than 5yrs	15	44.1
5-10 yrs	9	26.5
More than 10 yrs	8	23.5
5.5	2	5.9
Fever with rash		
Yes	1	2.9

No	33	97.1
Measles vaccination		
Yes	33	97.1
No	1	2.9
Other vaccines		
Fully immunised	11	32.4
Partially immunised	21	61.8
Non responders	1	2.9
Unimmunized	1	2.9
H/OChronic illness		
Yes	8	23.5
No	26	76.5

Table 11: Rubella titre

Rubella titre (IU/ml)	Frequency	Percent
Less than 7	25	73.5
7-13	1	2.9
More than 13	8	23.5
Total	34	100.0

Table 12: Measles titre

Measles titre	Frequency	Percent
Less than 0.9	17	50.0
0.9 - 1.1	4	11.8
More than 1.1	13	38.2
Total	34	100.0

Table 13: Rubella IgG antibody titre

Rubella IgG titre value	< 7 IU/ml	7-13 IU/ml	>13 IU/ml	Total
MR only	1	1	92	94
MR+ MMR	3	0	61	64
MMR only	3	1	18	22
Unimmunized	25	1	8	34

Table 14: Measles IgG antibody titre

Measles IgG titre value	<0.9 IU/mL	0.9-1.1 IU/mL	>1.1IU/mL	Total
MR only	12	14	68	94
MR+ MMR	13	9	42	64
MMR only	3	6	13	22
Unimmunized	17	4	13	34

In group A, those taken MR vaccine alone, 2 children showed low values which indicates the need of 2 doses of Rubella vaccine, however their measles titre was good. All children in group A had taken 9-month measles vaccine. 10 children were not fully immunised for age and 8/10 had low measles titre. 6 children had chronic illness and 1/6 had low measles titre. Among the seroprotected children, the levels of rubella antibody titres varied among the three groups A, B and C, according to their age. Highest titre values (>50 IU/ml) were noticed in the age group 4 to 5 years and 7 to 10 years in both groups A and B. The titre values were high (range 40-50 IU/mL) for those in the age group between 8 to 10 years followed by 2 to 5 years (range 30-40 IU/mL). In group C, those taken MMR alone, the rubella titre values were between 25 -40 IU/mL in 4 to 6 yrs age group. However both rubella and measles titre values were lower as the age increased, suggesting the need for a booster dose of the vaccine. In spite of receiving 2 vaccinations 3 children were not seroprotected against Rubella in group B, those taken MR+MMR. Only 26.4% were protected for rubella and 50% for

measles among the unimmunized children in group D. 97% of children had taken measles vaccine at 9 months in group D. That could be the reason for 50% protected against measles in group D. The rate of individuals in a population with doubtful protection (unvaccinated, non-responder and low responder after primary vaccination) prevents to reach the herd immunity of 95% necessary for elimination. The results of our serological studies strongly recommend re-vaccination against measles, mumps and rubella at 4 -6 years of age.

DISCUSSION

In the study performed by Redd et al. on children vaccinated with MMR, the seroconversion rates for measles and rubella were approximately 87% for children vaccinated at 9 months of age, 95% for those vaccinated at 12 months, and 98% for those who received the vaccination at 15 months of age^[24] Saffar et al. found the seroconversion rate for measles to be 90.5% but only 53% for rubella 4 – 8 weeks after primary vaccination with MMR in 12-month-old sero-negative infants^{.[25]} In a sample of

Singaporean children who received the MMR vaccination between 12 – 18 months of age, seroconversion rates for measles and rubella were reported to be 100%.^[26]

In a study conducted by Tabatabaei et al children vaccinated with MMR the seropositivity rates for rubella and measles were between 71 -75% within 4 – 7 weeks post-immunization.^[27]

In our study the majority had received MR vaccine between 5 to 10years of age. The duration since receiving MR vaccine at the time of enrolment varied from 5months to 15 months. In a study on immunity against Mumps in young adults, conducted by Patricia Kaaijk et al, CDC, in 2019 found that those who received a third dose of MMR(MMR-3) had increased antibody levels that may protect against Mumps virus infection for longer than previously assumed and is expected to be a good and safe intervention for controlling Mumps outbreak.^[28] According to CDC approximately 7% of people do not develop measles immunity after the first dose of vaccine. This occurs for a variety of reasons. In our study 50% of children were not protected after taking measles vaccination at 9months. CDC states About 97% of people develop immunity to measles after two doses of measles-containing vaccine(s/c measles +MR/MMR). But in our study 20% were not seroprotected even after taking both MMR and MR vaccine. This urges the need for a 3rddose of measles-rubella vaccine at 4 -6years of age which helps in preventing the decline of antibody levels as age advances and also contributes to prevent measles and rubella outbreak in the country. The most recent comprehensive The Advisory Committee on Immunization Practices (ACIP) recommendations for the use of MMR vaccine were published in 2013.According to that, MMR vaccine is recommended routinely for all children at age 12 through 15 months, with a second dose at age 4 through 6 years. The second dose of MMR can be given as early as 4 weeks (28 days) after the first dose and be counted as a valid dose if both doses were given after the child's first birthday. The second dose is not a booster, but rather is intended to produce immunity in the small number of people who fail to respond to the first dose.^[29,30]

CONCLUSION

97.5% of children who have taken MR vaccine have protective antibody against Rubella. The study shows that only 26.4% of unimmunised children are protected against Rubella. This may be attributed to their natural immunity. 73.6% of unimmunised children are not protected against Rubella. Substantial numbers of women are reaching childbearing age without immunity against rubella and thus are at a risk of passing the infection to their fetuses, who can then develop subsequent congenital defects leading to CRS. Various awareness drives

and campaigns conducted by the Ministry of Health, Kerala and Department of Health services, has immensely contributed in achieving 84% coverage for MR vaccination across the state. This immunization policy recommending rubella-containing vaccine like MR vaccination is highly desirable to prevent rubella and CRS. Inclusion of MMR in National Immunization Schedule as three doses would help in eliminating Measles and Rubella infection from our society. Despite good coverage rate with measles and rubella containing vaccine, significant numbers of vaccinated subjects were seronegative, possibly because of secondary vaccine failure. This may affect measles-rubella elimination goal in the country. Therefore more strengthening of regional/ national supplementary immunization activity should be considered.

If a child has received 2 doses of MMR vaccine, there is no need for an MR vaccine. However, there is also no harm in receiving an MR vaccine after having received complete MMR vaccination. If a child has received an incomplete (single dose) MMR vaccine, receiving the MR vaccine is necessary. The requirement of a third dose of MMR vaccine should also be considered.

Achievements, current scenario and future vision:

The Global Measles and Rubella Strategic Plan 2012-2020 (MRSP 2012-2020) period saw a significant reduction in the measles and rubella disease burden, a steep increase in the introduction of a second dose of measles containing (MCV2) and rubella vaccines, and improvements in surveillance. Rubella is being eliminated country by country with more babies protected in lower to middle income countries than ever before

By the end of 2018, 82 and 81 countries were verified as having eliminated measles and rubella, respectively. 178 WHO Member States introduced a second dose of measles-containing vaccine (MCV2) and 173 initiated rubella vaccination . Supplementary immunization activities and global coverage with MCV2 and Rubella 2 increased and surveillance quality improved.

But the number of reported measles cases increased globally in 2019.Preliminary global data show that measles cases rose by 300 percent in the first three months of 2019, compared to the same period in 2018 . In contrast to global trends, India has seen a reduction in measles and rubella cases in states, which have conducted the Measles and Rubella (MR) campaign. In 2019, a total of 1.2 million children did not receive measles-containing-vaccine(MCV1) in India, accounting for nearly half of the world's total along with the remaining five countries. Measles remains an important cause of morbidity and mortality, accounting for close to 9.7 million cases and more than 140,000 measles-related deaths in 2018. Rubella remains endemic in many countries and congenital rubella syndrome (CRS) continues to be reported with long-term consequences.

The measles and rubella strategic framework 2021-2030 (MRSF 2021-2030) aims to provide a high-level framework that will guide the development of regional and national strategies and operational plans. It will serve as a disease-specific strategy within the umbrella of the Immunization Agenda 2030 (IA2030). The Measles and Rubella Strategic Framework 2021-2030 envisions “A world free from measles and rubella”. The goal for the 2021-2030 period is to “achieve and sustain the regional measles and rubella elimination goals”.

The COVID-19 pandemic that started in late 2019, led to an interruption of routine vaccination services in many countries and cancellation or postponement of planned immunization agendas. As a result of COVID-19 as of June 2020, 29 countries have postponed measles campaigns, 18 of which are experiencing ongoing measles outbreaks. An additional 13 countries also postponed campaigns later in the year. Covid-19 has resulted in dangerous declines in immunisation coverage, leading to increased risk of measles outbreaks. This is why countries urgently need to prioritise measles “catch-up immunisation”.

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