Canterbury
District Health Board
Te Poari Hauora ō Waitaha

CORPORATE OFFICE

Level 1
32 Oxford Terrace
Christchurch Central
CHRISTCHURCH 8011

Telephone: 0064 3 364 4134
Kathleen.Smitheram@cdhb.health.nz;

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9(2)(a)
[redacted]

RE Official Information Act request CDHB 10780

I refer to your email dated 23 November 2021 to the Ministry of Health which they subsequently transferred to us on 14 December 2021 requesting the following information under the Official Information Act from Canterbury DHB. Specifically:

Immunisation Handbook 2020, Section 3.1.4.
Are the viruses in live vaccines transmissible?
There have been no recorded cases of measles mumps or rubella disease in individuals who were in contact with a vaccine recipient.
• Absence of evidence is not evidence of absence despite MOH IMAC claims that GEN-A measles is not measles because 'we say so' and it is not transmissible because 'we say so'
• Wording of the statement is inaccurate and imprecise, at best

The National Measles and Rubella Laboratory has responded to your claims and questions and has not contributed to the content of the New Zealand Immunization Handbook. However, we don't see any inaccuracy or imprecision in the wording of section 3.1.4, which purely talks about viruses in the live vaccine.

"Are the viruses in live vaccines, such as MMR and varicella, transmissible? These are highly attenuated (weakened) viruses designed specifically to induce an immune response without causing disease. There have been no recorded cases of measles, mumps or rubella disease in individuals who were in contact with a vaccine recipient."

In addition, section 4.3.1 mentions under "Measles, mumps and rubella vaccine" that

"MMR can be given to children and eligible adults who are in close contact with an immunocompromised individual. MMR vaccine viruses are considered non-transmissible; there is no evidence of the current MMR vaccine viruses being transmitted from vaccine recipients to a close contact" and the following publication is cited:

Greenwood et al., A systematic review of human-to-human transmission of measles vaccine virus. Vaccine, 2016. 34(23): p. 2531-6.

The Greenwood reference is a systematic review of 773 articles for genotypic confirmation of a vaccine virus transmitted from a recently vaccinated individual to a susceptible close contact. The conclusion was that "No evidence of human-to-human transmission of the measles vaccine virus has been reported amongst the thousands of clinical samples genotyped during outbreaks or endemic transmission and individual case studies worldwide".

In addition, Section 12.7 of the New Zealand Immunization Handbook mentions that:

"Following immunisation with both measles and rubella vaccines, live virus has been isolated rarely from pharyngeal secretions. There have been no confirmed cases of disease transmission from MMR vaccine viruses."

https://academic.oup.com/cid/article/58/9/1205/2895266
Results
The index patient had 2 doses of measles-containing vaccine;
of 88 contacts,
4 secondary patients were confirmed who had either 2 doses of measles-containing vaccine or a past positive measles IgG antibody.
All patients had laboratory confirmation of measles infection, clinical symptoms consistent with measles, and high-avidity IgG antibody characteristic of a secondary immune response.

It is unclear to us why this publication was cited? The publication "Outbreak of Measles Among Persons with Prior Evidence of Immunity, New York City, 2011 by Rosen at al. in Clinical Infectious Diseases 2014;58(9):1205-10" describes breakthrough infections as a result of secondary vaccine failure (i.e., vaccine failure due to waning of protective immunity and low levels of neutralizing antibodies), which has been documented for measles but remains rare. Although vaccination with 2 doses of MMR vaccine is highly effective and is a proxy for immunity to measles, cases of measles have occurred among persons despite receipt of 2 doses of MMR vaccine. There were three cases in the recent 2019 New Zealand outbreak with documented secondary vaccine failure, but no transmission was recorded from these cases. In addition, breakthrough cases due to secondary vaccine failure, appear to be attenuated (and usually don't cause further transmission) and are less likely to be hospitalised. The transmitted measles virus strain in the case described in the Rosen publication was a wild-type measles virus, genotype D4, not the vaccine strain genotype A.
I would suggest you have a look here:
https://asm.org/Articles/2019/July/Measles-Vaccination-and-Infection-Questions-and-Mi

1. **Provide all documentation and evidence in support of MOH statement section 3.1.4 that GEN-A strain of measles is not transmissible.**

See our answer above including reference to the Greenwood publication.

2. Provide all documentation and evidence in support of 2019 measles epidemic that lab confirmed GEN-A was not transferred from another vaccine recipient partially or fully vaccinated.

In the 2019 measles epidemic with over 2000 confirmed measles cases we identified the measles vaccine strain in 201 people that were mainly young children. All confirmed cases of the measles genotype A vaccine strain have had recent vaccination. None of these cases was unvaccinated. The data indicates that there was no transmission of the measles vaccine strain from a partially or fully vaccinated person to another unvaccinated person. As mentioned above, human-to-human transmission of the measles vaccine strain has never been reported in the literature.

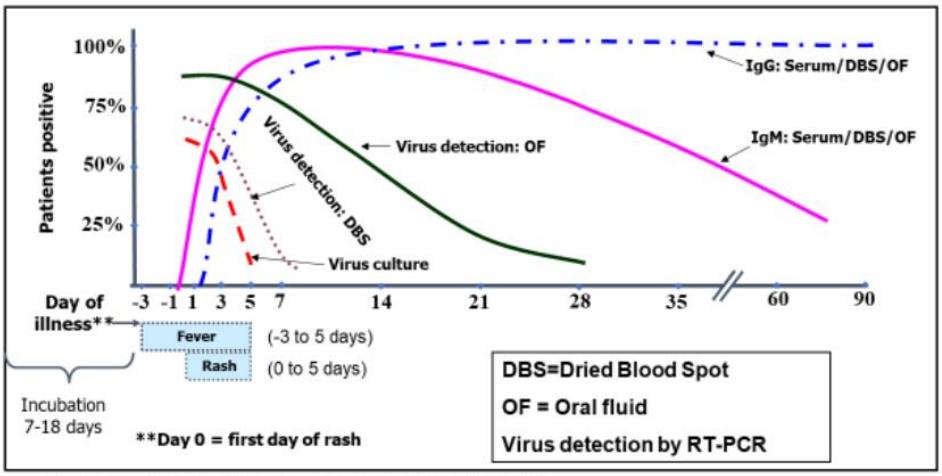
3. Provide all documentation and evidence in support of B3 or D8 strains not resulting from transmission by GEN-A strain. Provide all documents and evidence in support that B3 and D8 strains are not endemic in New Zealand.

The first part of your request is not quite clear to us.

- If you are asking for evidence that there are no cases of a vaccinated person (vaccinated with genotype A, MMR vaccine) being able to be infected by B3 or D8 wild-type strains and be able to transmit B3 or D8 wild-type strains?
    - Even though the measles genotype A vaccine strain is phylogenetically different from other wild-type measles viruses, the MMR vaccine shows a broad protection against infection with any other genotype (Fulton et al. Mutational Analysis of Measles Virus Suggest Constraints on Antigenic Variation of the Glycoproteins, Cell Report 11, 1331-1338, June 9, 2015). Because measles virus is antigenically monotypic (there are no antigenic variants or serotypes), antibodies generated against one genotype will bind and neutralize any other genotype. Therefore, vaccination confers protective immunity against all known genotypes, even though all vaccine strains are members of the single genotype A (Beaty and Lee, Constraints on the Genetic and Antigenetic Variability of Measles Virus, Viruses 2016, 8, 109). More importantly, despite the presence of different endemic genotypes, vaccination programs with standard measles vaccines have been successful in every country where they were performed adequately (Bankamp et al., Genetic Characterization of Measles Vaccine Strains, Journal of Infectious Diseases 2011;204:S533-S548). As mentioned before and described in the provided ASM link “Measles Vaccination and Infection: Questions and Misconceptions”, cases of primary and secondary vaccine failure can happen, but they are rare. Approximately 1% of people who fail to develop a protective immunity after receiving 2 MMR vaccines (primary vaccine failure) can contract measles if they travel to areas where the disease remains endemic or have contact with an infected person from a measles-endemic area. The rate of secondary vaccine failure (due to waning immunity) is even rarer. In most people vaccination appears to confer life-long protection.
- Or if you are asking if immunization with the measles vaccine strain genotype A can cause appearance and transmission of B3 or D8 strains?
    - No, this is impossible. The genotype A vaccine strain and the B3 and D8 wild-type strains are two completely different entities. The whole genomes (15,900 nucleotides) of the vaccine strain and the B3 and D8 wild-type strains have more than 500 differences on nucleotide level. The estimated genomic mutation rate for measles virus is 1.43 mutations per genome per replication (Schrag et al., Spontaneous Mutation Rate of Measles Virus: Direct Estimation based on Mutations Conferring Monoclonal Antibody Resistance, Journal of Virology, Jan 1999, p. 51-54). So, a vaccine strain would need to replicate approximately 390 times to accumulate all these nucleotide differences seen between vaccine strain and B3 or D8 wild-type strains. One replication cycle takes more than 14 hours = 0.6 days. For 390 replication cycles 227 days of continued replication would be necessary. However, replication of measles virus (wild-type or vaccine strain)

usually only occurs for a short period of time until IgM and IgG antibodies are generated that neutralize the virus (see red dashed line of positive virus culture in the graph below).

Figure 3.1 Schematic of wild-type measles virus infection and sensitivity of alternative sampling methods



* WER: 25, 2008, 83, 225–232 and MMWR: 2008; 57:657-660

Source: WHO Manual for the Laboratory-based Surveillance of Measles, Rubella, and Congenital Rubella Syndrome Chapter 3. Clinical specimens for the laboratory confirmation and molecular epidemiology of measles, rubella, and CRS.

In response to the second part of your question:
When a country is verified by the WHO Measles Regional Verification Commission as having eliminated measles, it means that the country interrupted transmission of the endemic strain of circulating measles virus for a period of 36 months. Importations of measles virus may have occurred during this period, but circulation of the imported strains of measles virus was interrupted within 12 months of the importation. Measles virus elimination is defined as the sustained interruption of transmission of endemic measles virus within a defined geographic region. Sustained endemic transmission is defined as an outbreak of more than 100 cases or ongoing transmission with a measles genotype of identical sequence for more than three months. Elimination does not imply that there is no virus within the defined region (this is eradication), but that the transmission of endemic virus has been eliminated (Kelly et al., WHO Criteria for Measles Elimination: A Critique with Reference to Criteria for Polio Elimination, Euro Surveillance, 2009 Dec 17;14(50):19445). New Zealand gained measles elimination status since 2017 verified by the WHO Measles Regional Verification Commission. In March/April 2019 New Zealand experienced the largest amount of notified measles cases in over a decade with more than 2000 notified cases. This was in fact not just one outbreak, but 15 separate outbreaks, caused by a combination of 7 different B3 wild-type strains and 5 different D8 wild-type strains due to several independent importations. The two biggest outbreaks had 226 cases (B3) and 459 cases (D8). Because these two longest outbreaks lasted less than 12 months, New Zealand has not lost its measles elimination status and B3 and D8 strains are not endemic in New Zealand.

4. Provide all documents and evidence for identification of multiple strains B3 D8 GEN-A (any combination) that were laboratory confirmed in individuals.

During the 2019 measles outbreaks we genotyped 134 B3 strains, 208 D8 strains and 201 samples containing the measles genotype A vaccine strain. No mixed sequences with two different genotypes were detected. All results were clear-cut either B3, D8 or genotype A.

Molecular epidemiology of measles viruses is an important component of outbreak investigations and is used for global surveillance of circulating wild–type measles strains. Measles virus genotyping can play

an important role in tracking transmission pathways during outbreak investigations. Genotyping results can help to confirm, disprove, or detect connections among cases. Genotyping can also distinguish whether a person has wild-type measles virus infection, or a rash caused by a recent measles vaccination. A small percentage of measles vaccine recipients experience rash and fever 10 to 14 days following vaccination. During outbreaks, measles vaccine is administered to help control the outbreak, and in these situations, vaccine reactions may be mistakenly classified as measles cases. About 5% of recently vaccinated persons develop symptoms of rash and fever. Because persons with vaccine reactions are not contagious, it is not necessary to conduct outbreak control measures such as contact investigations.
Source: https://www.cdc.gov/measles/lab-tools/genetic-analysis.html

5. Provide all documents and evidence that lab confirmed GEN-A strains were in vaccinated individuals only.

All 201 samples from the 2019 measles outbreak in which we have detected the measles genotype A vaccine strain were from recently vaccinated people.

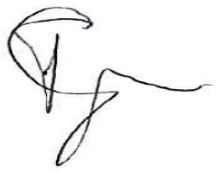
6. Provide all documents and evidence of unvaccinated individuals identified with GEN-A strain.

During the 2019 measles outbreak we haven't detected the measles genotype A vaccine strain in any unvaccinated individual.

I trust that this satisfies your interest in this matter.

Please note that this response, or an edited version of this response, may be published on the Canterbury DHB website after your receipt of this response.

Yours sincerely



Tracey Maisey
Executive Director
Planning, Funding & Decision Support