Optimising immunisation in children with 22q11 microdeletion

Dr Angela Berkhout

Queensland Children's Hospital in Brisbane

- Child Development Service cares for the majority of children with 22q11 microdeletion in Queensland.
- 148 children with 22q11 microdeletion known to the service
- Fortnightly clinic, review on 6-12 monthly basis

Immune Profile in children with 22q11 microdeletion

- Majority have a mild to moderate immunodeficiency or immune dysregulation.
- Minority have severe T cell immunodeficiency associated with complete athymia.
- No established guideline regarding immunological testing prior to live vaccine administration.
- Live vaccines can be safely administered if CD4 >0.5 CD3 >0.05 and CD8 >0.2 **and** normal mitogen response.

Sobh et al. (2016) Vaccination in primary immunodeficiency disorders. J Allergy Clin Immunol.

Hoffstetter et al (2014) Pediatrics	Multicentre retrospective cohort study, 194 subjects. CD4 <25% 33%, <15% 5%, >25% 66%; Abnormal mitogen response 31% normal 69%; TetAb/Dip Ab 26% 77% MMR vaccine 75% varicella vaccine; 58% completed by 19mo-35mo 14 unvaccinated subjects live vaccine preventable infections AEFI in 14% MMR and 20% VZV, no severe reaction.
Al-Sukaiti et al(2010) J Allergy Clin Immunol	Observational Study, 82 patients CD4 >500 cells/mm^3, CD8 normal in all but 1 patient, PHA reduced in 9 patients. No significant difference in seroconversion MMR 7.3% AEFI, no severe adverse reactions.
Azzari et al (2005) Vaccine	Retrospective cohort study, 14 patients CD4 15-37%, CD3 40-62% Seroconversion 22q11 vs control: measles (92.9% vs 96.3%) rubella (92.9% vs 100%) No severe AEFI reported
Moylett et al (2004) Clinical Immunology	Retrospective cohort study, 53 patients. 47% received live viral vaccines. Median CD3 40 cells/mm^3, CD4 26 cells/mm^3, CD8 12 cells/mm^3. PHA normal. 12% AEFI, no severe reactions.
Perez et al (2003) Pediatrics	Retrospective observational study, 59 patients, Children Hospital Philadelphia. CD3 1669-1759µ/L CD4: 1142 vs 1076 cellsµ/ L; CD8: 489 vs 503 cellsµ/ L 54% vaccinated VZV; 88% vaccinated MMR 63% unvaccinated children developed VZV disease 9% AEFI notification, no severe adverse reaction reported.
Iroh Tan et al (2015) Clin Pediatr	Retrospective study, 12 patients Mean CD8 512/mm^3 CD4 1034/mm^3; 83% had normal PHA 25% non-immunity HiB; all patients' immune tetanus/diphtheria

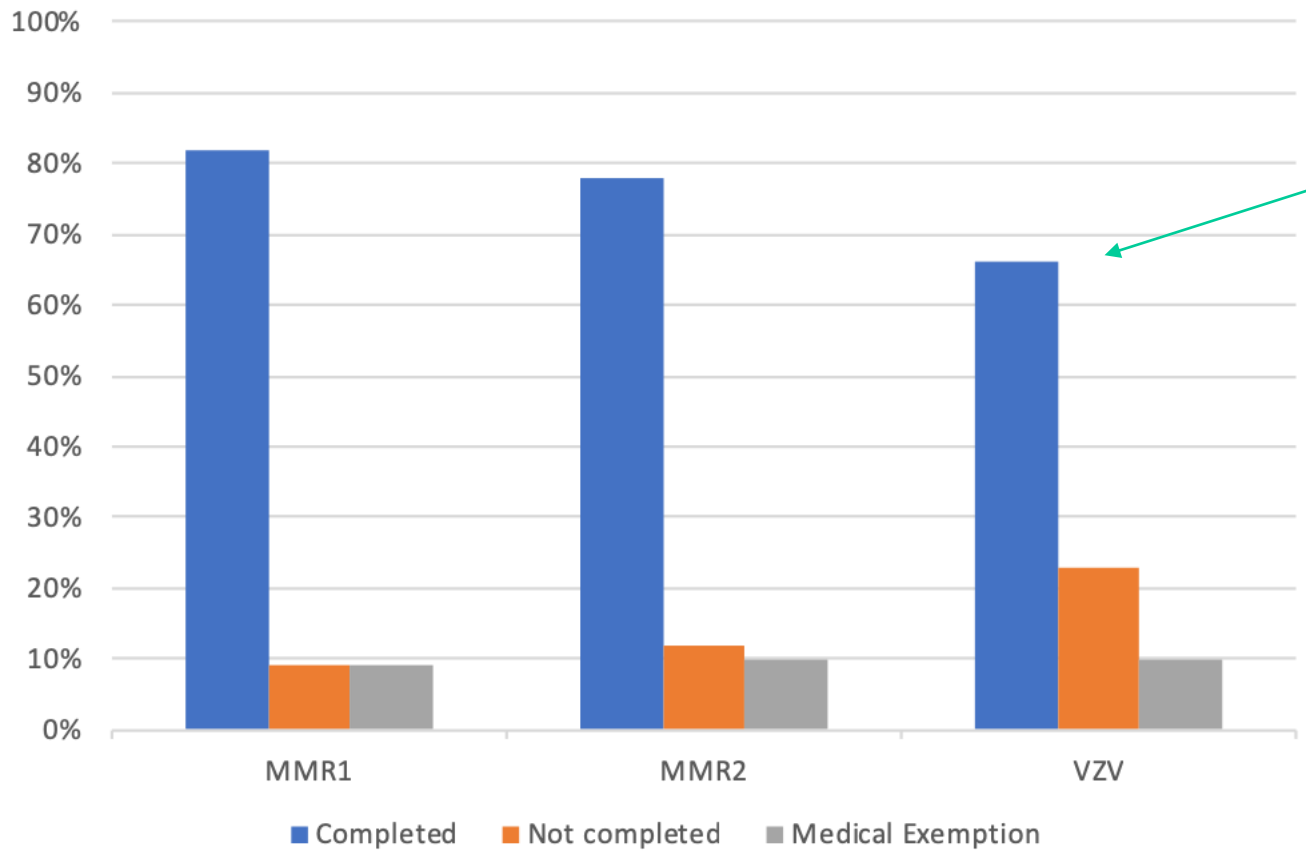
Hoffstetter et al (2014) Pediatrics	Multicentre retrospective cohort study, 194 subjects. CD4 <25% 33%, <15% 5%, >25% 66%; Abnormal mitogen response 31% normal 69%; TetAb/Dip Ab 26% 77% MMR vaccine 75% varicella vaccine; 58% completed by 19mo-35mo 14 unvaccinated subjects live vaccine preventable infections AEFI in 14% MMR and 20% VZV, no severe reaction.
Al-Sukaiti et al(2010) J Allergy Clin Immunol	Observational Study, 82 patients CD4 >500 cells/mm^3, CD8 normal in all but 1 patient, PHA reduced in 9 patients. No significant difference in seroconversion MMR 7.3% AEFI, no severe adverse reactions.
Azzari et al (2005) Vaccine	Retrospective cohort study, 14 patients CD4 15-37%, CD3 40-62% Seroconversion 22q11 vs control: measles (92.9% vs 96.3%) rubella (92.9% vs 100%) No severe AEFI reported
Moylett et al (2004) Clinical Immunology	Retrospective cohort study, 53 patients. 47% received live viral vaccines. Median CD3 40 cells/mm^3, CD4 26 cells/mm^3, CD8 12 cells/mm^3. PHA normal. 12% AEFI, no severe reactions.
Perez et al (2003) Pediatrics	Retrospective observational study, 59 patients, Children Hospital Philadelphia. CD3 1669-1759µ/L CD4: 1142 vs 1076 cellsµ/ L; CD8: 489 vs 503 cellsµ/ L 54% vaccinated VZV; 88% vaccinated MMR 63% unvaccinated children developed VZV disease 9% AEFI notification, no severe adverse reaction reported.
Iroh Tan et al (2015) Clin Pediatr	Retrospective study, 12 patients Mean CD8 512/mm^3 CD4 1034/mm^3; 83% had normal PHA 25% non-immunity HiB; all patients' immune tetanus/diphtheria

Hoffstetter et al (2014) Pediatrics	Multicentre retrospective cohort study, 194 subjects. CD4 <25% 33%, <15% 5%, >25% 66%; Abnormal mitogen response 31% normal 69%; TetAb/Dip Ab 26% 77% MMR vaccine 75% varicella vaccine; 58% completed by 19mo-35mo 14 unvaccinated subjects live vaccine preventable infections AEFI in 14% MMR and 20% VZV, no severe reaction.
Al-Sukaiti et al(2010) J Allergy Clin Immunol	Observational Study, 82 patients CD4 >500 cells/mm^3, CD8 normal in all but 1 patient, PHA reduced in 9 patients. No significant difference in seroconversion MMR 7.3% AEFI, no severe adverse reactions.
Azzari et al (2005) Vaccine	Retrospective cohort study, 14 patients CD4 15-37%, CD3 40-62% Seroconversion 22q11 vs control: measles (92.9% vs 96.3%) rubella (92.9% vs 100%) No severe AEFI reported
Moylett et al (2004) Clinical Immunology	Retrospective cohort study, 53 patients. 47% received live viral vaccines. Median CD3 40 cells/mm^3, CD4 26 cells/mm^3, CD8 12 cells/mm^3. PHA normal. 12% AEFI, no severe reactions.
Perez et al (2003) Pediatrics	Retrospective observational study, 59 patients, Children Hospital Philadelphia. CD3 1669-1759µ/L CD4: 1142 vs 1076 cellsµ/ L; CD8: 489 vs 503 cellsµ/ L 54% vaccinated VZV; 88% vaccinated MMR 63% unvaccinated children developed VZV disease 9% AEFI notification, no severe adverse reaction reported.
Iroh Tan et al (2015) Clin Pediatr	Retrospective study, 12 patients Mean CD8 512/mm^3 CD4 1034/mm^3; 83% had normal PHA 25% non-immunity HiB; all patients' immune tetanus/diphtheria

Methods:

- 134 children (0-18 years) with 22q11 microdeletion known to Child Development Service between 2000 to 2018
  - Immunisation history including live vaccines and additional doses of pneumococcal vaccine
  - Immunology work up proceeding live vaccine administration
  - Adverse Events Following Immunisation (AEFI) notifications

Live Vaccination Status in 22q11 cohort:

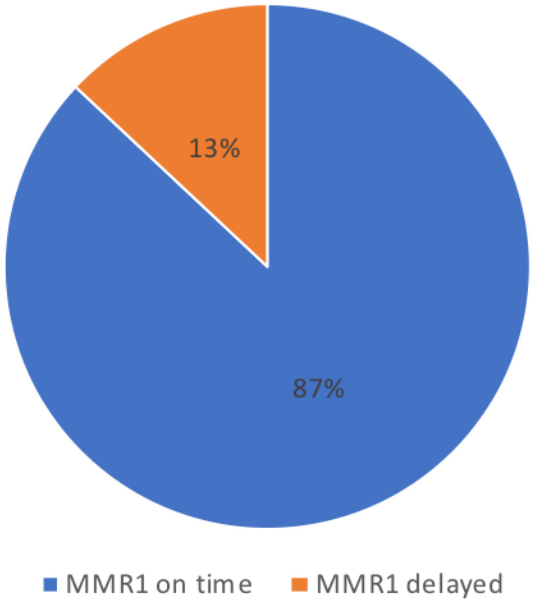


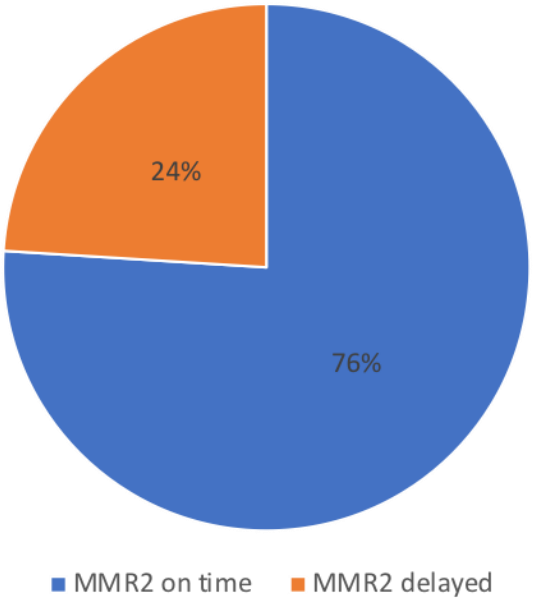
VZV introduced Australian NIP 2005 (11 patients)

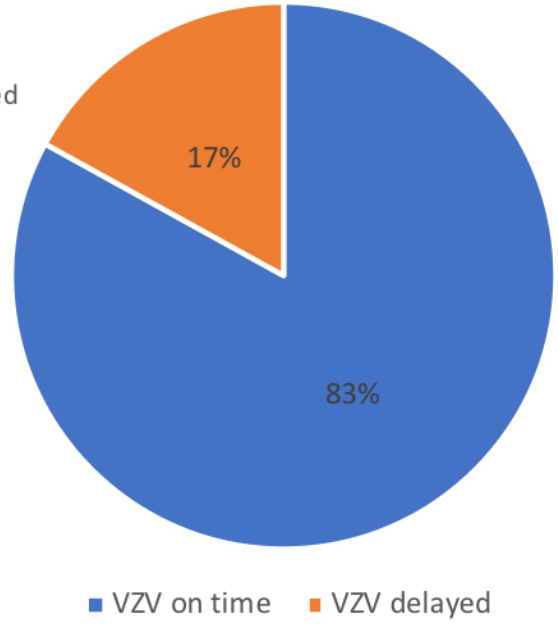
VZV disease

	Completed	Not completed	Medical Exemption
MMR1	82% (102/124)	9% (11/124)	9% (11/124)
MMR2	77% (96/124)	12% (15/124)	10% (13/124)
VZV	66% (82/124)	23% (29/124)	10% (13/124)

Timeliness of live vaccination administration:



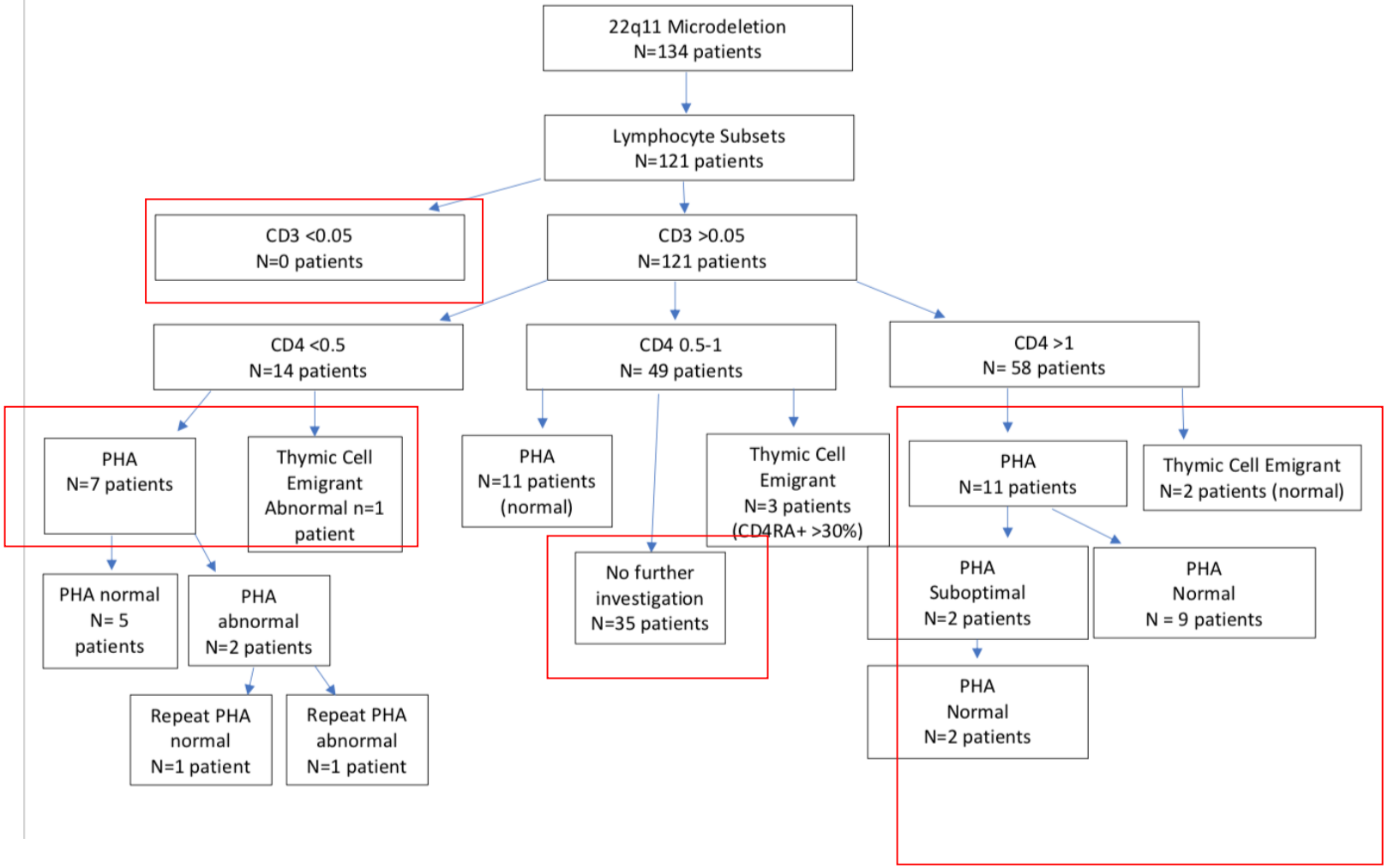




** On time defined as within a 6 month window

	MMR 1 not complete	MMR 1 Medical Exemption	MMR 2 not complete	MMR 2 Medical Exemption	VZV Not complete	VZV Medical Exemption
Number Patients	11/124 (9%)	11/124 (9%)	15/124 (12%)	13/124 (10%)	29/124 (22%)	13/124 (10%)
CD4 <0.5 and CD8<0.3	2/11	2/10	2/15	2/12	4/28	2/12
Dip/Tet Ab Non-immune	0/5	0/7	0/7	1/9	0/14	1/9
Abnormal PHA	2/5	1/4	3/6	1/5	3/10	1/5
Repeat PHA Abnormal	0/2	1/4	0/3	1/1	0/3	0/0

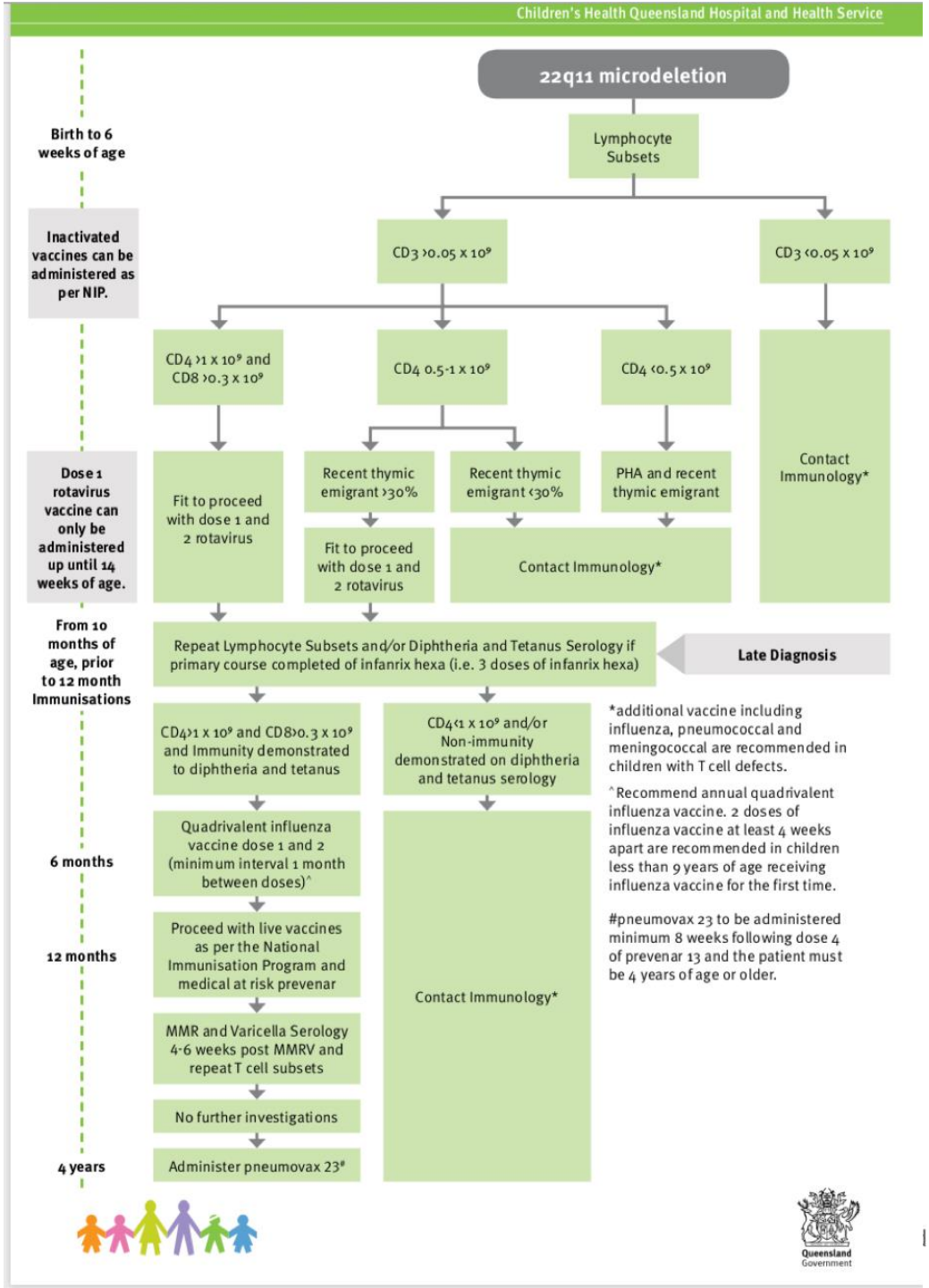
Immunology Investigations:



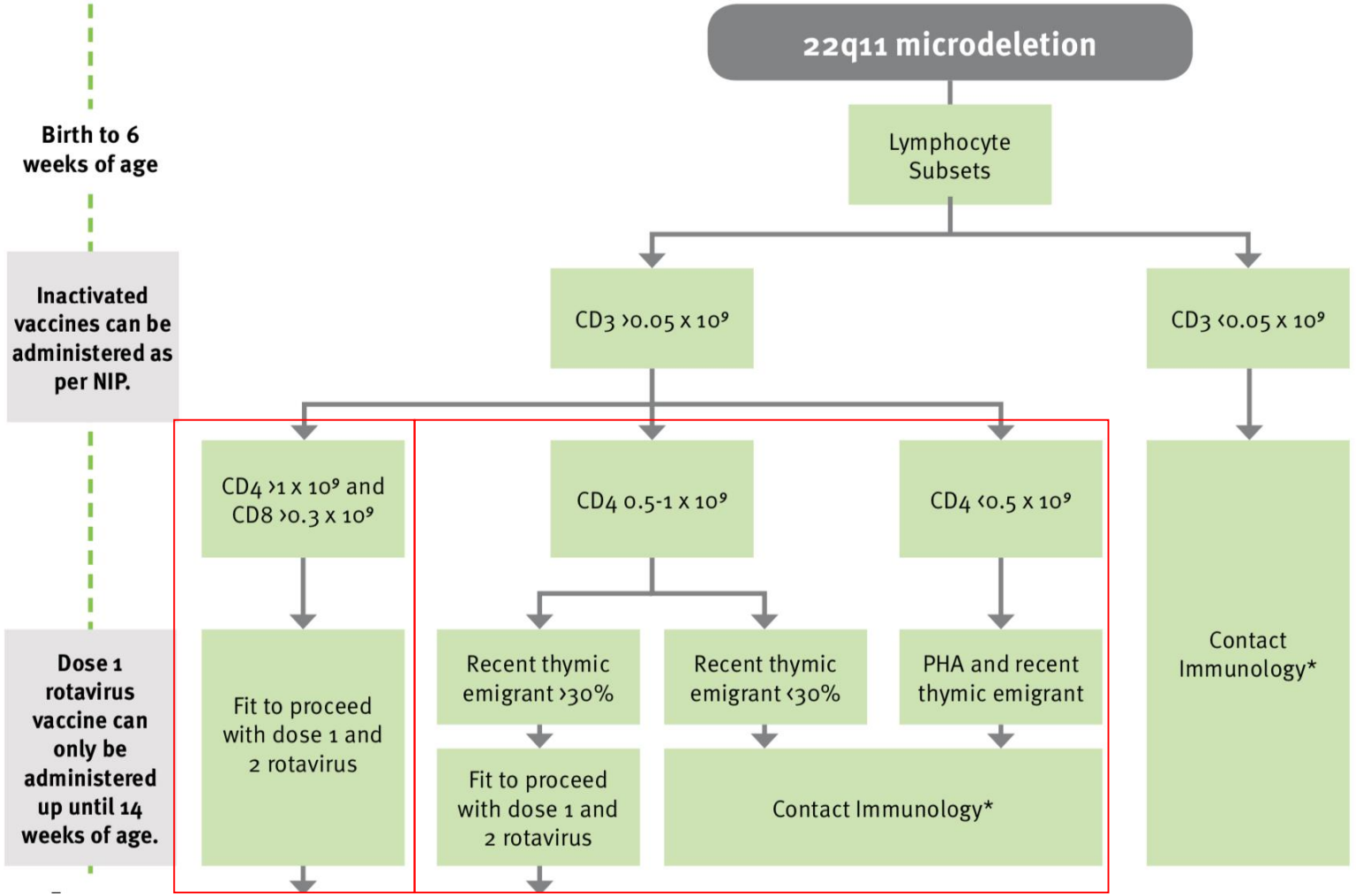
No Adverse Event Following Immunisation Notifications

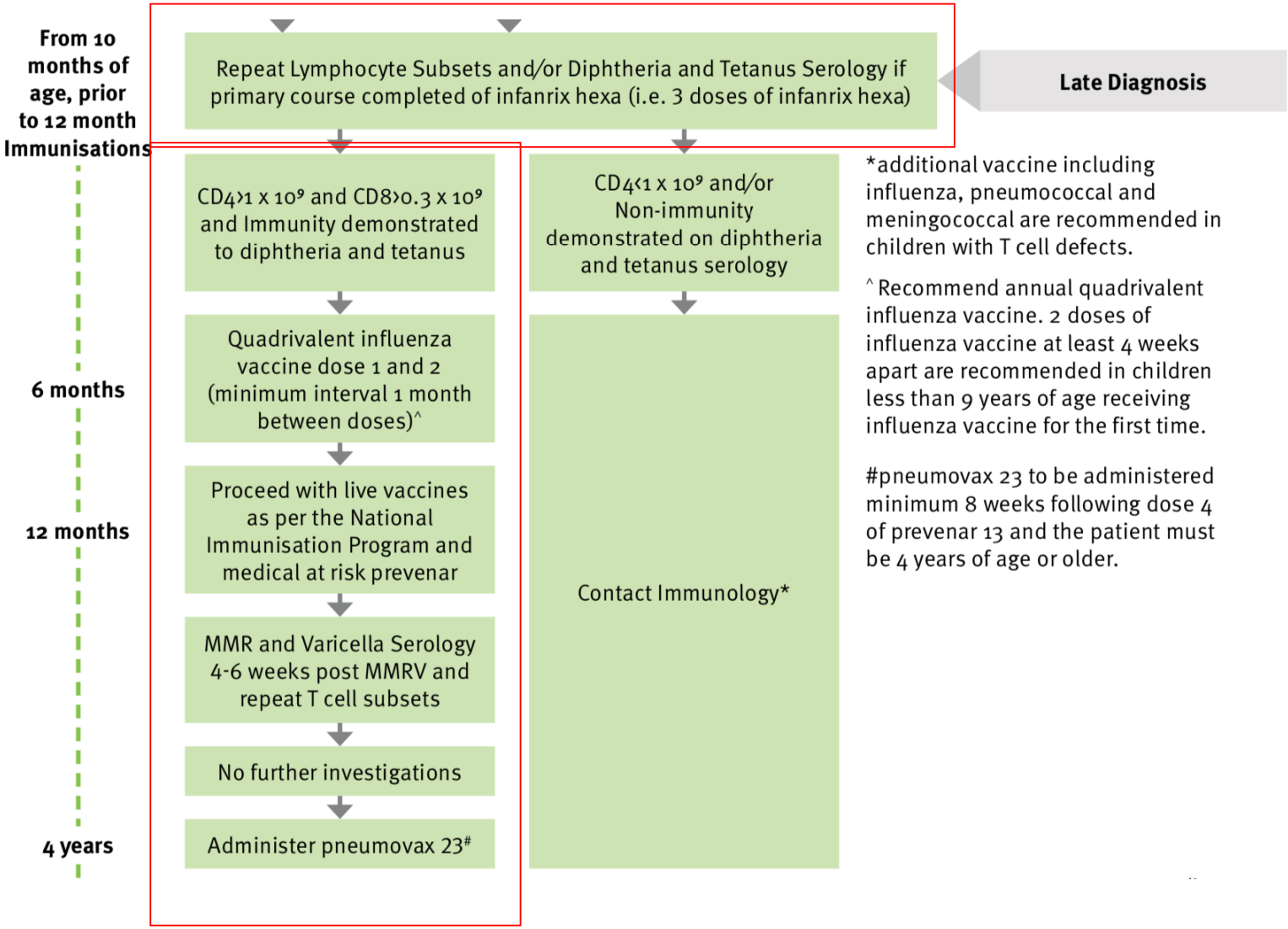
	MMR1	MMR2	VZV
AEFI Notification	0/102	0/96	0/82

	MMR1	MMR2	Varicella	AEFI
CD4 <0.5 and CD8 <0.3	2	2	2	Nil reported
Dip/TetAb non immune	7	6	6	Nil reported
Abnormal PHA	1	1	1	Nil reported



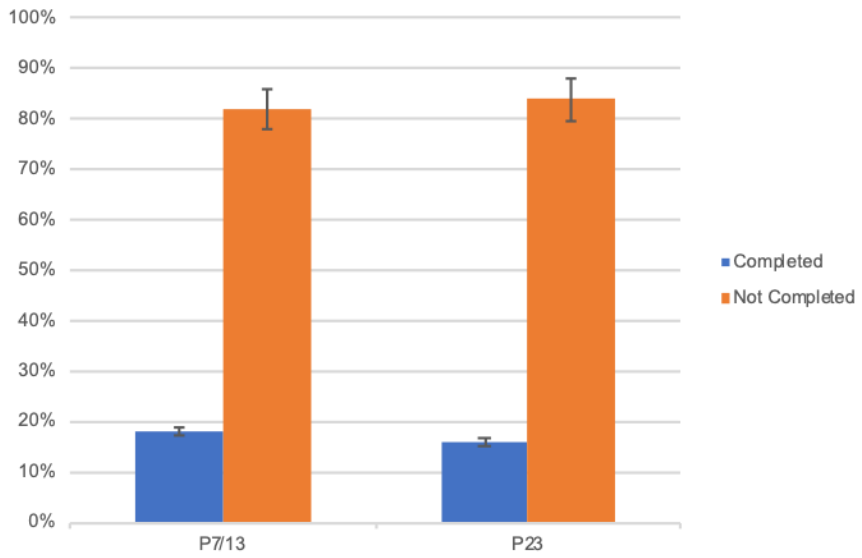
Queensland Government


22q11 microdeletion
Lymphocyte Subsets
Birth to 6 weeks of age
Inactivated vaccines can be administered as per NIP.
CD3 >0.05 x 10⁹
CD3 <0.05 x 10⁹
CD4 >1 x 10⁹ and CD8 >0.3 x 10⁹
CD4 0.5-1 x 10⁹
CD4 <0.5 x 10⁹
Dose 1 rotavirus vaccine can only be administered up until 14 weeks of age.
Fit to proceed with dose 1 and 2 rotavirus
Recent thymic emigrant >30%
Recent thymic emigrant <30%
PHA and recent thymic emigrant
Contact Immunology*
Fit to proceed with dose 1 and 2 rotavirus
Contact Immunology*


From 10 months of age, prior to 12 month Immunisations
Repeat Lymphocyte Subsets and/or Diphtheria and Tetanus Serology if primary course completed of infanrix hexa (i.e. 3 doses of infanrix hexa)
Late Diagnosis
CD4>1 x 10⁹ and CD8>0.3 x 10⁹ and Immunity demonstrated to diphtheria and tetanus
CD4<1 x 10⁹ and/or Non-immunity demonstrated on diphtheria and tetanus serology
6 months
Quadrivalent influenza vaccine dose 1 and 2 (minimum interval 1 month between doses)^
12 months
Proceed with live vaccines as per the National Immunisation Program and medical at risk prevenar
MMR and Varicella Serology 4-6 weeks post MMRV and repeat T cell subsets
Contact Immunology*
No further investigations
4 years
Administer pneumovax 23#
*additional vaccine including influenza, pneumococcal and meningococcal are recommended in children with T cell defects.
^ Recommend annual quadrivalent influenza vaccine. 2 doses of influenza vaccine at least 4 weeks apart are recommended in children less than 9 years of age receiving influenza vaccine for the first time.
#pneumovax 23 to be administered minimum 8 weeks following dose 4 of prevenar 13 and the patient must be 4 years of age or older.

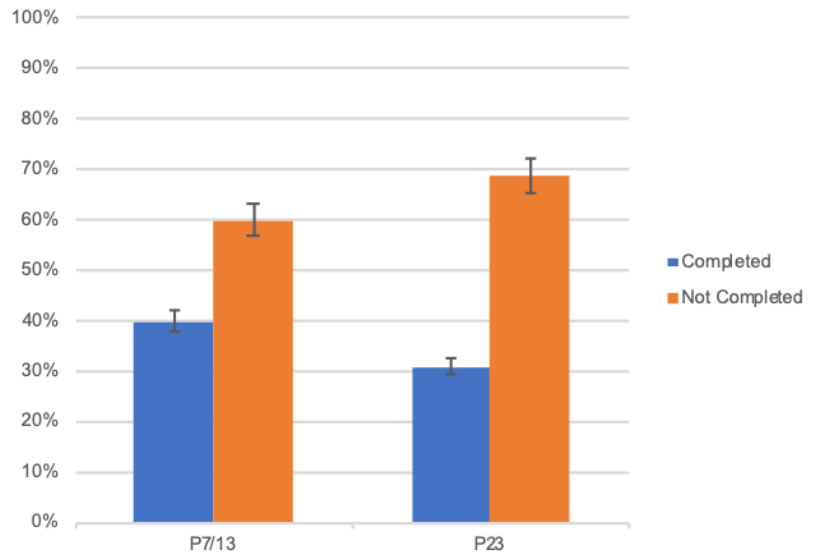
Medical At Risk Pneumococcal Coverage

PRE GUIDELINE



	Complete	Not complete
P7/P13	18%	82%
P23	16%	84%

POST GUIDELINE



	Complete	Not complete
P7/P13	40%	60%
P23	31%	69%

Conclusion

- Live vaccination can be safely administered in patients with 22q11 microdeletion despite evidence of mild to moderate immunosuppression.
- There are significant variations in live vaccine practices in this patient cohort as well as the immunology work up received prior to live vaccine administration.
- Further studies are required to support guidelines for immunology investigation prior to live vaccine administration.

Acknowledgements

Dr Sophie Wen, Paediatric Infectious Disease Physician, QCH

and

Dr Kahn Preece, Paediatric Immunologist, The John Hunter Hospital, Newcastle

and

Dr Vinita Prasad, Developmental Paediatrician, Child Development Service, QCH

and

Dr Honey Heussler, Director Child Development Service, QCH

and

Dr Alberto Pinzon, Paediatric Immunologist, QCH

and

Dr Julia Clark, Director Paediatric Infectious Diseases, QCH

and

Dr Vanil Varghese, General Paediatrician, QCH

Any Questions???

References

1.Bassett et al. Practical Guidelines for managing patients with 22q11.2 deletion syndrome. The Journal of Pediatrics. 2011;159(2):332-9

2.Sullivan K. Chromosome 22q11.2 deletion syndrome and DiGeorge syndrome. Immunol Review. 2019;287(1):186-201

3.Hofstetter et al. Live vaccine use and safety in DiGeorge Syndrome. Pediatrics. 2014;133(4):946-54

4.Sobh et al. Vaccination in primary immunodeficiency disorders. J Allergy Clin Immunol. 2016;4(6)1066-75

5.Iroh Tram et al. Vaccine responses and immunologic characteristics of pediatric patients with DiGeorge Syndrome. Clin Pediatr. 2015;54(13):1290-2.

6.Al-Sukaiti et al. Safety and efficacy of MMR vaccine in patients with DiGeorge Syndrome. J Allergy Clin Immunol. 2010;126(4):868-9.

7.Azzari et al. Safety and immunogenicity of MMR vaccine in children with congenital immunodeficiency (DiGeorge Syndrome). Vaccine. 2005;23:1668-71.

8.Moylett et al Live viral vaccine sin patients with partial DiGeorge syndrome: clinical experience and cellular immunity. Clinical Immunology. 2004;112:106-12.

9.Sullivan et al. Longitudinal analysis of lymphocyte function and numbers in the first year of life in chromosome 22q11.2 deletion syndrome. Clinical & diagnostic laboratory immunology. 1999;6(6):906-11

10. Sullivan et al. Live viral vaccines in patients with DiGeorge Syndrome. Clinical Immunology. 2004;113:3.

11. Perez et al. Safety of live viral vaccines in patients with chromosome 22q11.2 deletion syndrome. Pediatrics. 2003;112(4):325-7.