



VIRCLIA MEASLES IGG ASSAY EXPERIENCE

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Oct 2019

MEASLES

WELLINGTON SCL



- Auckland & NZ is currently experiencing a measles outbreak — ref NZ Herald 10 Oct 2019

New targeted approach for measles outbreak as 1327 cases confirmed

"We are now at a very high rate of disease occurrence and we need to be more targeted."



Two unborn babies die after mothers catch measles during pregnancy

Auckland Regional Public Health Service to give an update on Auckland's measles outbreak



Measles outbreak: Father's kiss of near death should be warning to others, wife says

Father's long recovery after being exposed to an individual for less than a few minutes.



Auckland measles outbreak has peaked, cases now declining

Auckland Regional Public Health Service is addressing media about the measles outbreak.

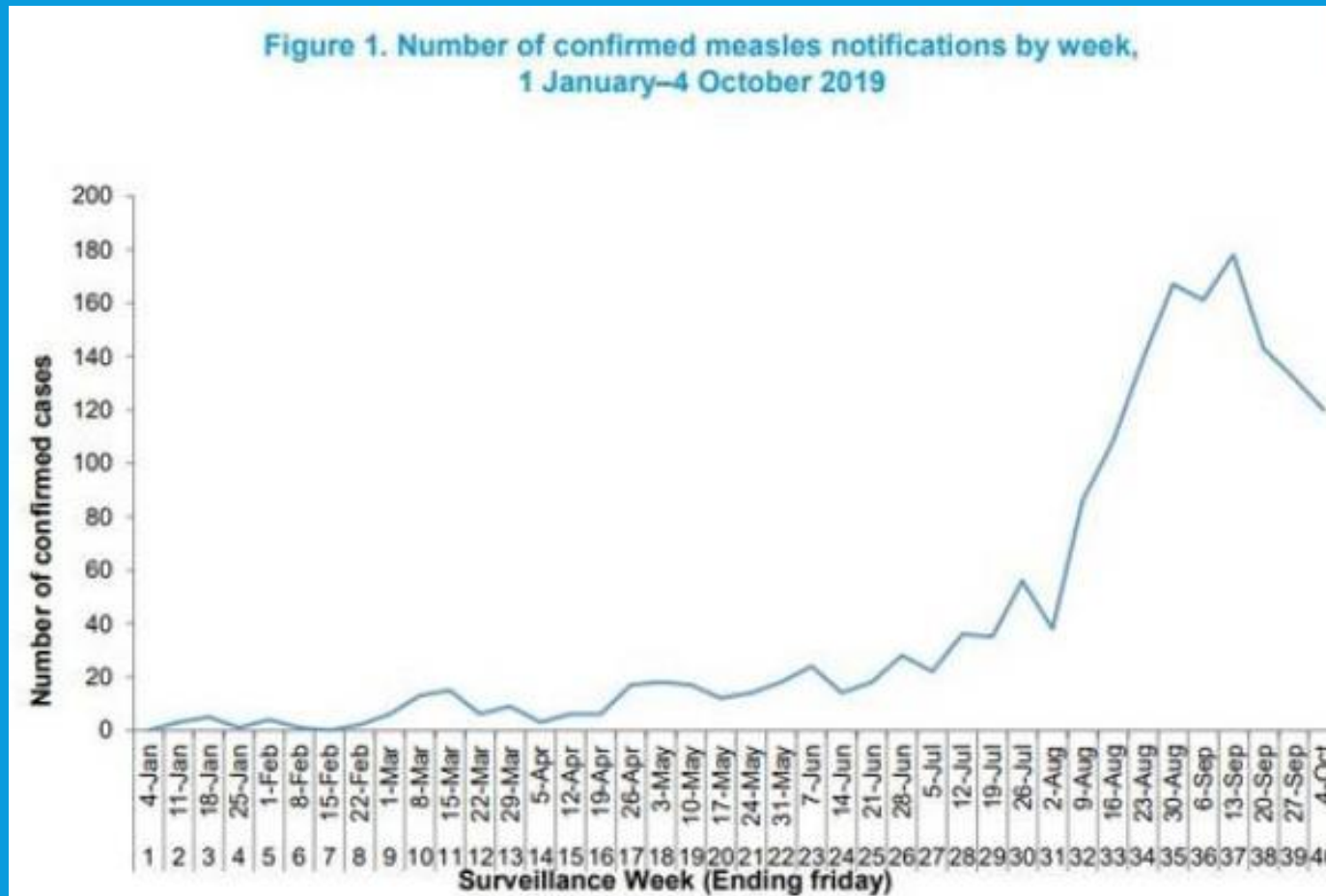
Measles outbreak: Why are some vaccinated people still getting sick?

There will always be a few people who don't develop immunity, health authorities say.

MEASLES



- Cases NZ wide — ref NZ Herald 10 Oct 2019



MEASLES IGG



- VirClia Thunderbolt validation initially performed Dec 2017
- Concern was initially raised with Microbiologists that VirClia Measles IgG may be giving false positives
- Validation performed on consensus samples - Trinity ELISA, EuroImmune ELISA and miniVidas Measles IgG all agreeing

Measles VirClia IgG Concordance		
Assay	VirClia Monospot Measles IgG	Cutoff
Reference	Concensus Measles IgG Trinity/EuroImmune/Vidas	Neg <=0.9 Equ 0.91-1.09 Pos >=1.1
	Concensus ELISA Neg	Concensus ELISA Pos
VirClia Neg	11	0
VirClia Pos	12	19
Total	42	
Concordance	71.4%	
Specificity	47.8%	
Sensitivity	100.0%	

MEASLES IGG ? FALSE POS



- National Immunisation Register begun in Dec 2005 in NZ
- Retrieved “spare” serum on children under 14 after routine biochemistry blood tests.
- The MMR vaccination status was reviewed by Microbiology Registrar, recorded as partial 1 MMR dose, full 2 MMR doses, no record or no vaccination.
- 27 samples were collected
- 5 – partially vaccinated - all Measles IgG Positive by Vidas & VirClia
- 16 – fully vaccinated - all Measles IgG Positive by Vidas & VirClia
- 2 – no vaccination status records - Measles IgG Positive by Vidas & VirClia
- 4 – unvaccinated – Measles IgG Negative by Vidas & VirClia – no false positives

MEASLES IGG ? FALSE POS



- Vaccination rates by 5 years age Q4 2017 CCDHB 89.5%, Wairarapa, 94.5%, HV 93.0% - average of 92.3%
- NZ home grown free of Measles and Rubella according to WHO. Since 2012 all cases have originated overseas
- No evidence of “False Positive” VirClia Measles IgG in the few unvaccinated patient samples found
- Microbiologist thought the VirClia Measles IgG positivity rate better reflects the known high vaccination rate in Wgtn region and therefore happy to implement use of VirClia Measles IgG assay with manufacturers cutoffs
- Implemented from Aug 2018

MEASLES IGG



- 2019 RCPA sample P1 1E – result arrived
- Deemed a routine Immune status check - pooled serum
- Consensus 92% Neg from 90 labs
- 13 methodologies

Biomerieux 12, Biorad 5, DiaSorin 43, Diesse 1, EuroImmune 6, Hemagen, 1 NovaTec 2, Sekisui,1 Siemens 4, Trinity Biotech 7, Vircell 4, Virion, 3, Zeus 1

MEASLES IGG



- RPCA P1 1E – we got a low level positive – consistent with other Vircell VirClia Thunderbolt users
- Siemens IgG Elisa – I’m told is deemed WHO “gold standard” ELISA IgG assay – 2 of 4 users gave as IgG Equivocal
- Breakdown by methodologies used – 13 in total
 - Biomerieux 1/12, Biorad 5, DiaSorin 4/3, Diesse 1, EuroImmune 6, Hemagen, 1/1 NovaTec 2, Sekisui 1, Siemens 2/4, Trinity Biotech 7, Vircell 3/4, Virion 3, Zeus 1
- “VirClia untested” RPCA Vaccine Preventable Measles samples from 2018 when VirClia not in use performed and within consensus
- RCPA P1 1E failure - coincided with Measles outbreak in Christchurch NZ
- Testing for Measles IgG changed from solely “Immune Status” checks (mainly Occupational Health screens) to also include “Contact Tracing” of people exposed to known Measles cases

MEASLES IGG



- Microbiologists discussed with local Regional Public Health doctors who manage all contact tracing etc “that assay was out of concensus on latest RCPA”.
- First Measles infection occurs locally in Wgtn a few weeks after receiving the RCPA report
- Regional Public Health perform contact tracing and can legally quarantine people as required
- The financial impact on families of quarantining someone can be high, especially if they don’t have sufficient sick leave etc.
- Agreed with RPH that all weak (initially ISR 3.0 or less) VirClia Measles IgG will be sent to a sister lab (use Trinity Biotech ELISA) for testing to check if any changes have occurred from initial assay validation in Dec 2017 – 43 samples performed
- Similar result comparison outcome obtained from when initial validation performed
- VirClia ISR >2 correlated with Trinity ELISA Positive or Equivocal

MEASLES IGG



- Contact tracing - approx. 50 patients of initial measles case in Wellington
- 17 of these gave VirClia Measles IgG between 1.1 and 3.0 “deemed Equivocal” rather than Detected as per PI (Did not want to call people Immune if there was doubt)
- These patients all had unknown MMR vaccination status, many non NZ immigrants.
- 5 Positive by Trinity, 3 Equivocal by Trinity, 9 Negative by Trinity
- RPH reviewed outcome of Equivocal Measles Immunity contacts of this initial index Measles cases
- Initially no patients with results reported as “Equivocal by VirClia Measles IgG” had gone on to get Measles infection despite documented high risk exposures.
- RPH allowing contacts with Equivocal Measles IgG “out of home quarantine” with advice of “ if you get measles symptoms” stay home and ring your GP or Public health
- Quarantine – starts 7 days post “exposure” eg recent case person with measles was at school only on Monday 16th Sept (too sick to be at school rest of the week). So staff & students who aren’t protected are in home quarantine from Monday 23rd till Monday 30th Inclusive

MEASLES IGG

WELLINGTON REGION MEASLES CASES

Regional Public Health
 HAUORA Ā IWI KI TE ŌPOKŌ • O TE IKA A MĀUI
 Better health for the greater Wellington region

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Bay of Plenty



Week 18

- Part of NZ wide outbreak (100 cases)
- 2 cases
- 11 contacts



51 Contact Interactions

- NO FURTHER CASES -



Melbourne



Week 21

- On holiday from Melbourne
- 9 cases (One in Mid Central)
- 73 contacts



303 Contact Interactions

- NO FURTHER CASES -



Singapore



Week 23

- On holiday from Singapore
- 6 cases
- 18 contacts



117 Contact Interactions
316 Contact Interactions
157 Contact Interactions
86 Contact Interactions



- NO FURTHER CASES -



Not a measles case



Confirmed measles case

MEASLES IGG



▪ Stop Press

- On Thursday heard from RPH on outcome of 2 patients reported with Equivocal Measles IgG from a recent contact tracing
- Both from Kiribati. Attended same wedding in Auckland, sat beside a cousin who then diagnosed with measles. Both given MMR vaccine as presented within 72 hours as per post exposure prophylaxis procedures.
- Patient 1 – Measles IgG ISR 1.44 17/09/19, reported as Equivocal.
 - 13 days later on 30/09/19 presented with “rash & fevers but clinically not likely measles”
 - Measles PCR performed and was positive. Sent for Measles genotype – not genotype A as in MMR vaccine
- Patient 2 - Measles IgG ISR 1.45 16/09/19 Tested again 15 days later as still in contact with patient 1 . Measles IgG ISR 11.46 – demonstrating Measles IgG seroconversion – no measles symptoms

The Ministry of Health says although MMR is highly effective against measles, a few people will not have an immune response to the vaccine.

But if enough people are immunised, those few will be protected as they are unlikely to come into contact with the disease. This is known as [herd immunity](#).

MEASLES IGG

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- Effectively we have established our own “Equivocal Range” or Reference Interval / Clinical decision value as per ISO15189:2012 5.5.2 recommendation
- Our VirClia Measles IgG “Equivocal” range now set from 0.9 – 2.0 ISR and reported with a qualifying comment
 - “Equivocal IgG levels indicate protective immunity under most circumstances, please discuss with clinical microbiologist if there has been contact with a confirmed or probable measles case.”

HEV

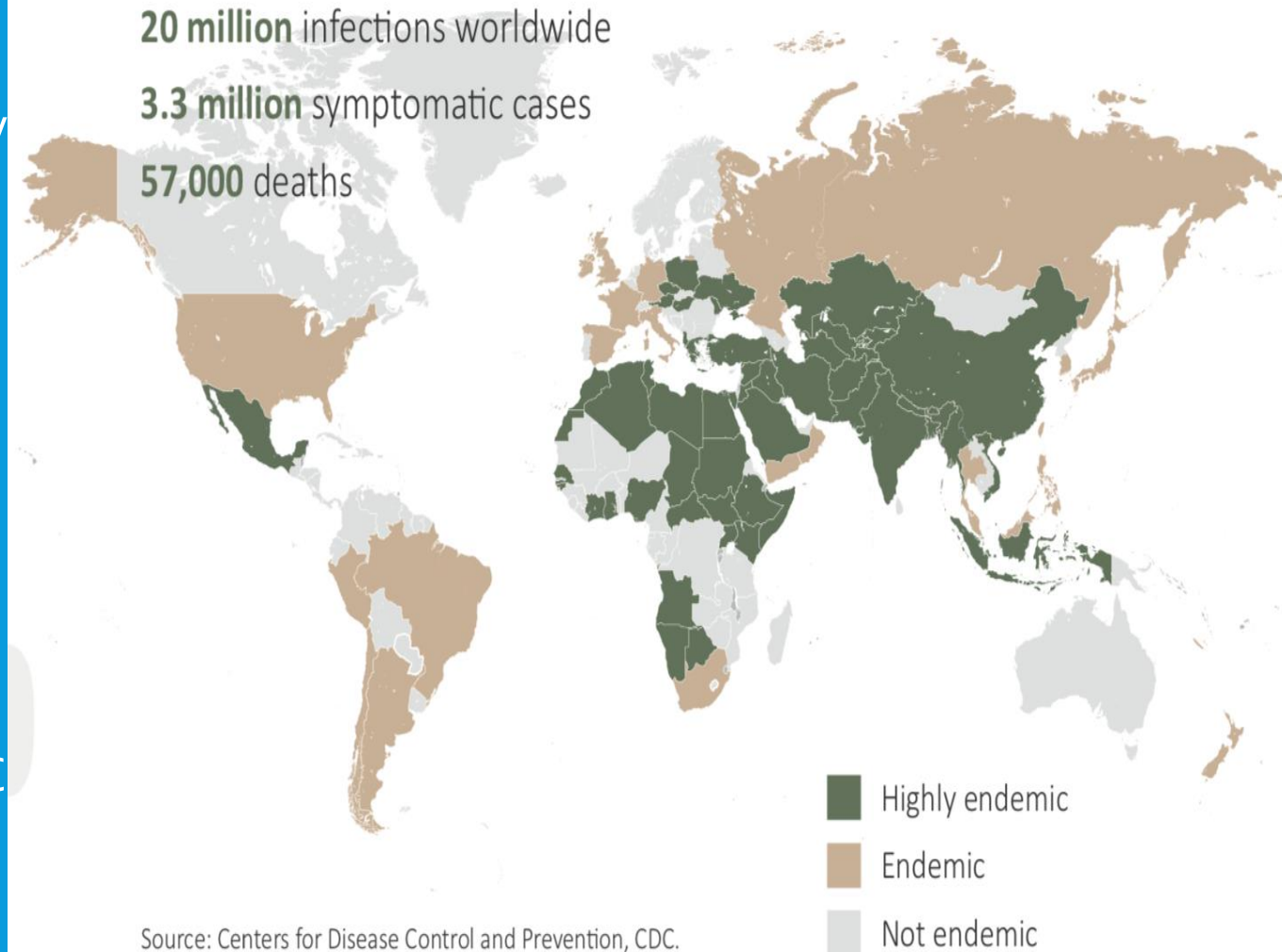


- Enteric infections with a similar course to Hepatitis A
- Globally one of the most common causes of acute viral illness
- Large majority of disease burden is in Asia and Africa – 60% of all infections occur in East and South Asia
- Estimated 20 million HEV infections worldwide, 3.3 million estimated to be symptomatic and 56,000 HEV related deaths
- Pregnancy - in their third trimester of pregnancy, a more severe infection increased maternal and foetal mortality and morbidity, up to 25%. Cause unknown but the theory is that suppression of T-cell mediated immunity render them more susceptible.
- Zoonotic transmission occurs from pigs, undercooked deer and wild boar meat

HEV IN NZ



- According to Hewitt et al, the seroprevalence in NZ blood donors was 9.7% using the Wantai HEV IgG ELISA and 8.1% using the MP Diagnostics HEV IgG ELISA 4.0.
- HEV RNA was not detected in any of the samples tested, indicating no evidence of current infection in any blood donors.
- HEV seroprevalence rates were similar to the HEV seroprevalence rates determined in blood donors from other developed countries:
- US (7.7%), Australia (6%), Ireland (5.3%), and England Northern Wales (10%)
- Positivity rates increased with age
- HEV is classed as endemic in NZ according to CDC

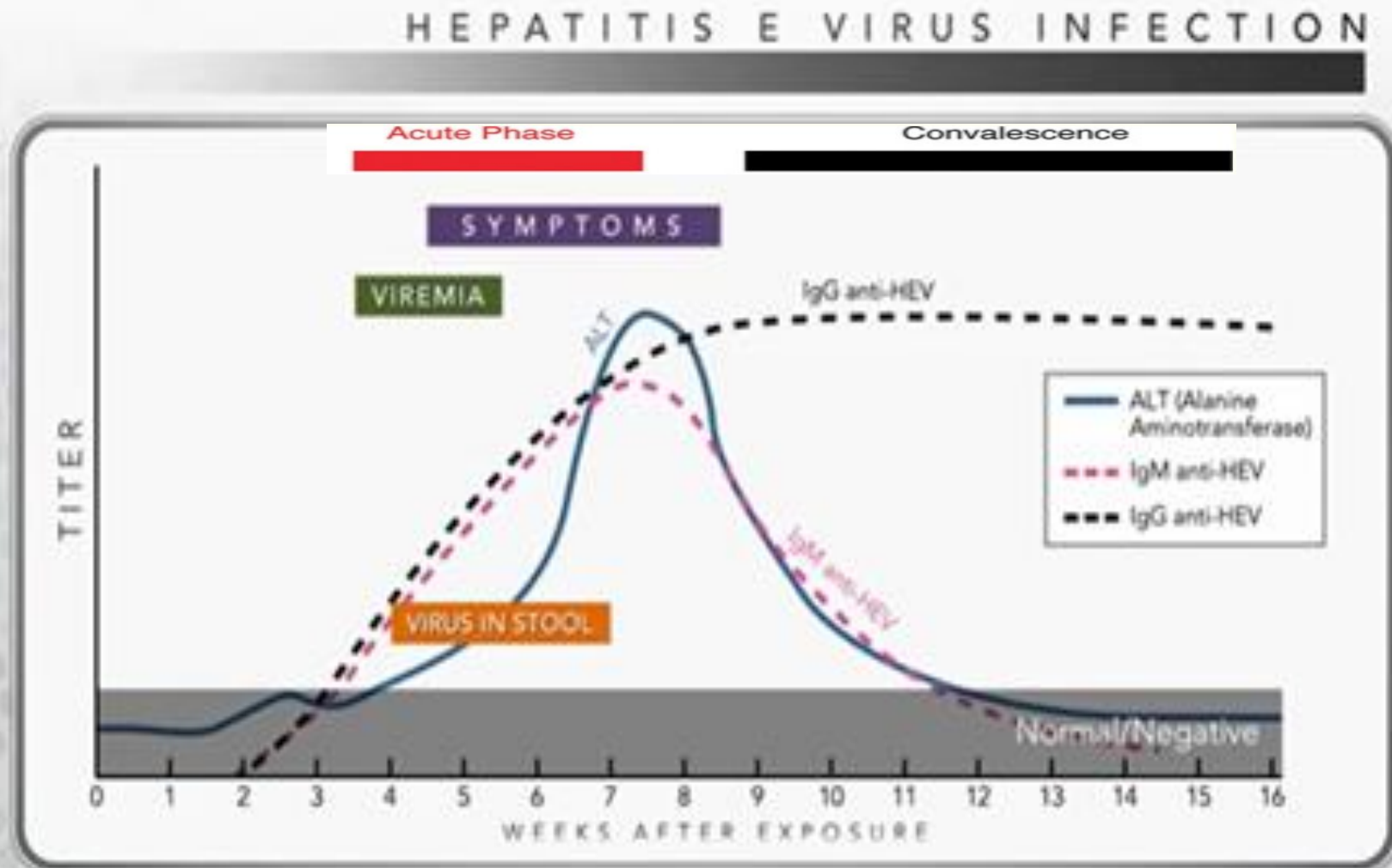


Source: Centers for Disease Control and Prevention, CDC.

COURSE OF INFECTION



- Incubation period: 2 – 8 weeks following exposure, average of 40 days
- Elevation of liver enzymes usually occurs 4-5 weeks after exposure to HEV and persist for 3 to 13 weeks
- Viremia can be detected 3 weeks after exposure or a week prior to onset of symptoms, and last for about two weeks.
- Excretion of virus in stools vary but usually last for one week before symptoms appear, and slow down at the onset of symptoms within 2-3 weeks.
- No Serology available in NZ



VALIDATION OF VIRCLIA ASSAYS



- HEV IgG

Hep E VirClia IgG Concordance

		Cutoff	
Assay	VirClia Monospot Hep E IgG	Neg <=0.9	Equ 0.91-1.10
Reference	ESR Hep E IgG IgG	Pos >=1.1	
		Neg/Pos	
	Concensus EIA Neg	Concensus EIA Pos	
VirClia Neg	11	0	
VirClia Pos	0	24	
Total	35		
Concordance	100.0%		
Specificity	100.0%		
Sensitivity	100.0%		

- HEV IgM – update chart data

Hep E VirClia IgM Concordance

		Cutoff	
Assay	VirClia Monospot Hep E IgM	Neg <=0.9	Equ 0.91-1.10
Reference	ESR Hep E PCR Neg/RCPA	Pos >=1.1	
		Neg/Pos	
	PCR Neg	RCPA Concensus Pos	
VirClia Neg	34	0	
VirClia Pos	0	2	
Total	36		
Concordance	100.0%		
Specificity	100.0%		
Sensitivity	100.0%		

VALIDATION OF VIRCLIA ASSAYS

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Cross Reactivity HEV IgM

HEV IgM	HEV IgM S/Co	HEV IgG	HEV IgG S/co		
Negative	0.027	Negative	0.157	EBV	VCA IgM 11.77, VCA IgG 37.0, EBNA IgG 2.8
Negative	0.022	Negative	0.054	EBV	VCA IgM 34.01, VCA IgG 1.71, EBNA IgG 0.01
Negative	0.014	Positive	7.671	EBV	VCA IgM 1.41, VCA IgG 0.11, EBNA IgG 0.01
Negative	0.021	Negative	0.067	TOX	Toxo IgM 22.3 IgG 165
Negative	0.02	Positive	2.606	TOX	Toxo IgM 44.7 IgG >650
Negative	0.155	Negative	0.389	CMV	CMV IgM 2.15 IgG 457
Negative	0.033	Negative	0.024	HBV	HBsAg 6198, Anti-HBc IgM >200 HBeAg 3.8 anti-Hbe 0.00
Negative	0.033	Negative	0.042	MEASLES	Measles IgM 5.4 PCR Pos
Negative	0.02	Negative	0.106	VARICELLA	VZV IgM 3.01
Negative	0.035	Negative	0.05	HEP A	Hep A IgM 14.5
Negative	0.112	Negative	0.503	HEP C	Hep C Agen Pos
Negative	0.016	Positive	7.891	SYPHILIS	Syph RPR Pos 1:128
Negative	0.059	pos	2.641	RF	RF High >650

VALIDATION OF VIRCLIA ASSAYS



- Leptospirosis IgM verse CHL IgM screen

- Lepto IgM verse ESR MAT confirmation

Leptospira VirClia IgM Concordance			
		Cutoff	
Assay	VirClia Monospot Lepto IgM	Neg <=0.9	Equ 0.91-1.10 Pos >=1.1
Reference	CHL Lepto IgM	Neg/Pos	
	VirClia Lepto IgM Neg	VirClia Lepto IgM Pos	
CHL IgM ELISA Neg	4	1	
CHL IgM ELISA Pos	1	3	
Total	9		
Concordance	77.8%		
Specificity	80.0%		
Sensitivity	75.0%		

Leptospira VirClia IgM Concordance			
		Cutoff	
Assay	VirClia Monospot Lepto IgM	Neg <=0.9	Equ 0.91-1.10 Pos >=1.1
Reference	ESR Lepto MAT	Neg/Pos	
	VirClia Lepto IgM Neg	VirClia Lepto IgM Pos	
ESR/RCPA MAT Neg	8	7	
ESR/RCPA MAT Pos	0	8	
Total	23		
Concordance	69.6%		
Specificity	100.0%		
Sensitivity	53.3%		

REFERENCES & ACKNOWLEDGEMENT

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