Paediatric Vaccines RESEARCH REVIEW™

MEASLES SPECIAL

Making Education Easy

Issue 40 – 2019

In this issue:

Abbreviations used in this issue
Ig = immunoglobulin
SAGE = Strategic Advisory Group of Experts
WHO = World Health Organization

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Welcome to the latest issue of Paediatric Vaccines Research Review.

Due to the current measles epidemic in NZ this issue is devoted entirely to measles infection and vaccination, with an interesting selection of local and international studies.

We hope you find the issue informative and look forward to any feedback you may have.

Kind regards,

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A measles epidemic in New Zealand: why did this occur and how can we prevent it occurring again?

Authors: Turner N

Summary: NZ has seen a huge increase in measles cases this year, with more cases reported in 2019 than during any year in the past 2 decades. This article discussed reasons for the outbreak and described various management strategies that were implemented in response to it.

Comment (NT): This year NZ has experienced the largest upsurge in measles cases for more than 2 decades. With multiple imports and outbreaks all around the country this is clearly an epidemic. More than 80% of cases have been in metropolitan Auckland, mostly Counties Manukau, affecting predominantly infants and young children, followed by adolescents and young adults, with very high rates for Pacific people. Overall complication rates are around 22%, which is in line with international experience in high-income countries. However, we have experienced a very high hospitalisation rate, particularly for infants. This I suggest is more likely to be around conservative management in a country that has previously little experience with measles. Why so much measles this year? Three separate reasons. Firstly, there are increasing outbreaks internationally which lead to increased importations. There is a lot of traffic in and out of NZ! Secondly, NZ historically did poorly in effectively delivering our childhood immunisation programme, and even worse for Māori and Pacific communities. Now we are doing a lot better, but we suffer the historical legacy of having large numbers of un- and under-immunised young and midlife adults. Thirdly, there has been slippage in our infant programme in the past 3 years, particularly affecting Māori and low-income infants. What do we need to do? Closing historical immunity gaps requires a mass outreach campaign to young and midlife adults – a group not historically desperate to rush in to get vaccinated, but the recent high media attention should help. It will require reaching out to all those under-vaccinated or with unknown records, alongside raising awareness and innovative broadening of access to services, including increasing use of pharmacy and occupational health. Also, our infant programme urgently needs a bit of revitalisation. We have complacently accepted a good immunisation programme for many years, without recognising attention and resourcing does need to increase. Primary care is stretched, and the immunisation programme has increased in complexity. Outreach services report how difficult it is out there with all the challenges associated with worsening poverty for many families, housing insecurity, mobility and multiple life stressors. A lot of media attention has been focussed on the anti-immunisation voice and their effect on vaccine hesitancy. Decline rates overall have increased by 1–1.5% since 2017. This issue is important to be aware of, but it is not the major issue and we need to take care we do not overemphasise the place and voice of anti-immunsation sentiment. Strengthening and supporting the system to deliver a quality service alongside enabling the best possible access to services for high-needs communities is the starting point for creating an environment where immunisation is the positive choice for our community.

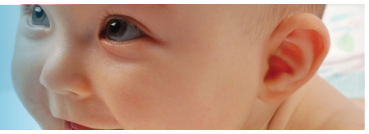
Reference: NZ Med J 2019;132(1504):8-12
Abstract

Independent commentary provided by Associate Professor Nikki Turner.

Nikki is an academic General Practitioner. She works as an Associate Professor for the University of Auckland and part-time as a General Practitioner in Wellington. Nikki's academic interests are in primary health care, preventive child health and immunisation. Amongst other roles, she is a member of the WHO Strategic Advisory Group of Experts (SAGE) committee on immunisation. **For full bio CLICK HERE.**

Independent commentary provided by Dr Helen Petousis-Harris.

Helen is Senior Lecturer in the Department of General Practice and Primary Health Care at the University of Auckland and the Director of the Vaccine Datalink and Research Group. **For full bio CLICK HERE.**



Meeting of the Strategic Advisory Group of Experts (SAGE) on Immunization

Summary: The WHO Director-General established the Strategic Advisory Group of Experts (SAGE) on Immunisation in 1999. It is the principal advisory group to the WHO for vaccines and immunisation, and met in October 2019 to discuss shortfalls in measles eradication, among other issues. A full report of the meeting will be published on 29 November 2019.

Comment (NT): Eradication is the reduction of the global incidence of a disease to zero as a result of deliberate efforts. At the 70th World Health Assembly held in May 2017 the Director-General of the WHO was requested to report back on the feasibility of measles and rubella eradication. The WHO SAGE concluded in 2010 that measles can and should be eradicated and a formal goal and target date should be set based on measurable progress. Eradication is complex, due to the multi-dimensions beyond just biological, but also politics, economics, social considerations, technical, operational, and programme issues. Interestingly, rubella will be easier to eradicate with lower coverage levels than measles as it is such a highly effective antigen, so as we focus on measles, we will gain rubella eradication. But for measles, current global vaccination coverage is insufficient and has stagnated at around 86% for dose 1 and under 70% for dose 2. Significant international outbreaks this year have highlighted the fragility of gains making the reality very sobering. This October SAGE meeting reviewed this issue and concluded that achieving measles eradication is not realistic without significant further effort. If the world wanted to do it, we could. However, as we still have not managed the home straight of polio eradication we are clearly not yet ready. What would it take? "*Efforts to achieve and maintain measles and rubella elimination must be based on substantial strengthening of primary health care systems that are effective in delivering routine immunization.*" It simply means that if every country delivered an effective and equitable immunisation programme we would succeed. We could do this. We absolutely know it would immeasurably improve the lives of children everywhere, but is the world willing to equitably put the effort in? Where do our values lie?

Reference: Wkly Epidemiol Rec 2019; published online Nov 29
Abstract

Is the global measles resurgence a "public health emergency of international concern"?

Authors: Durrheim D et al.

Summary: The International Health Regulations (IHR) were developed in 2007 and are legally binding in all countries. In the IHR, a public health emergency of international concern (PHEIC) is defined as "an extraordinary event that may constitute a public health risk to other countries through international spread of disease and may require an international coordinated response". This article discussed whether or not the current global measles resurgence should be declared a PHEIC.

Comment (NT): The advantage of having a PHEIC declared is that it gets focused public attention and mobilisation of extraordinary resources for what is then seen as an acute public health risk that threatens the world. To date there have been 5 PHEICs declared: 2009 pandemic flu; polio in 2014, Ebola in 2014, Zika in 2016, and Ebola again in 2019. Measles can be eradicated. The barriers to eradication are around political and social engagement and willingness. The Americas have proven the ability to eradicate, achieving measles elimination for the entire region in 2017. Their subsequent loss of elimination status was a result of spread from other parts of the world entering and embedding back into Venezuela following the collapse of the health service, allowing spread from external imports. Dave Durrheim and team make a strong case for considering measles for a PHEIC in the context of the 2019 global measles resurgence. The 2019 PHEIC is based around the Ebola outbreak in the Democratic Republic of the Congo (DRC). It is sobering to note that the DRC has higher rates of measles currently than Ebola – the world freaks out with the terrifying nature of Ebola, however measles is killing more children at higher rates. So why do we not create an international emergency for measles? Measles persists because health services are inequitable and inadequate. World attention to measles means a world focus on improving healthcare systems and reducing equity gaps in every country. A PHEIC would help focus the attention we need here.

Reference: Int J Infect Dis 2019;83:95-7
Abstract

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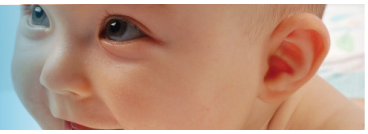

The introduction of 'No jab, No school' policy and the refinement of measles immunisation strategies in high-income countries

Authors: Trentini F et al.

Summary: This modelling study predicted measles immunity profiles over the next 30 years in 7 high-income countries (Australia, Ireland, Italy, Singapore, South Korea, UK and US). Under current vaccination policies, the model showed that the susceptible fraction of the population would remain below the measles elimination threshold only in Singapore and South Korea. In Australia, Ireland, the UK and US, maintaining the level of susceptible individuals at <7.5% up to 2050 would require either an increase in coverage of routine programmes to >95% or the introduction of compulsory vaccination at school entry (with >40% coverage).

Comment (NT): Measles outbreaks internationally have resurged this year. This is a direct result of low vaccination coverage resulting in low herd immunity. Obtaining and maintaining coverage levels of at least 95% with relatively homogenous update is a hard ask for many countries, including NZ. This modelling shows the majority of countries will need further 'catch up and follow up' to achieve this. School entry checks for vaccination are a recommendation of the WHO. Our US colleagues report that school entry checks were a vital component of their measles elimination achievement. So again this question arises, is there a role for mandation in the NZ context? I am on record many times with concerns that poorly thought-out mandatory policies such as highly targeting beneficiaries do more damage than help by creating polarisation and punishing the most vulnerable – those who are more in need of support not whips. But the rights of our community to keep our children safe are equally important. There are other ways of considering this issue. NZ already has legislation to allow for checking records at early childcare and school entry. This has never been properly resourced or effectively applied. We need a process of checking all children at enrollment, followed by a formal process of communicating with the families of the under-vaccinated, offering ease of access to services, and then a formal process of decline for the small percentage who, after having been offered all appropriate services, still chose to decline. A less draconian process offered with appropriate access and support I believe will achieve the aims in a more mature way. This is a country that believes in immunisation as the norm, offers ease of access to information and services, follows a clear process and allows dissent once appropriate communication and services have been fairly offered. Having said that, we also need to recognise that there are localities that have much higher rates of decline. These need resourcing urgently for further targeted services to ascertain the root of the issues – is there mistrust and why; what are the community conversations and how can health services engage in them (such as with tailored immunisation programmes). The social media amplification factor of misinformation also needs addressing and it is positive to see recent international discussion and action around the more responsible management of internet and other social media forums.

Reference: BMC Med 2019;17:86
Abstract

Emergence of attenuated measles illness among IgG-positive/IgM-negative measles cases, Victoria, Australia, 2008-2017

Authors: Gibney K et al.

Summary: This Australian study evaluated the epidemiological, clinical, and laboratory profile of measles cases with waning immunity. 190 measles cases reported to Victoria's Department of Health and Human Services in 2008–2017 were classified according to serology at diagnosis: IgG– (non-immune; 79% of cases); IgG+/IgM+ (indeterminate; 14%); or IgG+/IgM– (waning immunity; 7%). Between 2008 and 2017, the proportion of cases with waning immunity increased from 0% to 13% (p<0.001). Seven (54%) waning immunity cases reported receiving a measles-containing vaccine. Compared with nonimmune and indeterminate cases, those with waning immunity were more likely to be male, less likely to report fever, coryza, and cough, and had lower virus burden.

Comment (NT): For those of us who would like absolute certainty, sorry but science does not work like that. Does full vaccination ensure lifelong protection against measles? Probably, but not always. Breakthrough measles cases in those who are fully vaccinated do occur, but are uncommon and the majority of cases occur because of primary failure, i.e. the recipient did not respond to vaccine in the first place. However, there are cases of measles seen in those who have had an immune response to a vaccine, but the immunity has since waned sufficiently to cause disease. It is reassuring that most of these cases result in more mild disease (attenuated) and the viral burden is lower so they can transmit disease but less commonly. As a country moves toward elimination and measles is not circulating there is less opportunity to obtain immunity from exposure to measles, so the effects of waning immunity become more important. While numerically these cases are low numbers the policy answer lies in sustaining overall high coverage to maintain herd immunity. Would we ever consider a third dose to boost immunity? Not at this stage with small numbers, but time will tell. I think there is a much stronger argument for boosting mumps immunity. Mumps is not as strong an antigen, and breakthrough disease is more common as we have been seeing recently in NZ.

Reference: Clin Infect Dis 2019; published online May 6
Abstract

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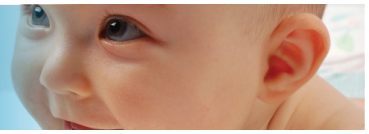
Trans-endocytosis elicited by nectins transfers cytoplasmic cargo, including infectious material, between cells

Authors: Generous A et al.

Summary: This article described a newly discovered process that facilitates the transfer of cytoplasmic cargo (including infectious measles virus material) from epithelial cells to neurons. The process is called nectin-elicited cytoplasm transfer (NECT), and may be exploited by pathogens to extend tropism.

Comment (HPH): Do you ever wonder during a measles epidemic when we will inevitably see a case of subacute sclerosing panencephalitis (SSPE)? After all, just like our epidemic, it is possible we might see this happen given the incidence is about 1 per 10,000 cases and more likely in younger patients. In fact the risk for infants has been estimated to be as high as 1 in 600. A contemporary study from Germany estimated the risk in children under 5 to be 1 per 1700–3300, or basically the same as acute fatal measles infection. Given that SSPE is always fatal it is a scary prospect. SSPE progresses slowly causing memory loss, irritability, loss of motor control, sometimes seizure and blindness, followed by death within 1–3 years. Awful! How does measles virus infect the brain and persist? Given the virus does not appear to have a way to access these brain cells (remember it is more into B cells and epithelial cells) researchers have been at a loss to explain how it ends up in the brain. In this study the investigators showed that where certain types of cells became juxtaposed one ripped a piece off the other and took it up, not just a chunk of the membrane but also a sip of the inside of the cell (the cytoplasm). They proposed that measles might take advantage of this process to jump from epithelial cells to neurons. By tracking fluorescing measles virus, they showed it moving from the epithelial cells into the neurons via this nifty transfer process. Measles can't access neurons on its own because it does not have the right 'key'. However, using this method it simply hitches a ride. SSPE has been vanishing as measles elimination progresses. However, when we communicate about the risks of measles infection, overlooking the rare but very real complication is easy but perhaps worth keeping on the radar because the risk to the individual patient is still the same.

Reference: J Cell Sci 2019;132(16):jcs235507
Abstract



Measles virus infection diminishes preexisting antibodies that offer protection from other pathogens

Authors: Mina M et al.

Summary: This study evaluated the long-term impact of measles virus infection on the immune system. 77 unvaccinated children were assessed by VirScan (an assay that tracks antibodies to thousands of pathogen epitopes in blood) before and 2 months after natural measles virus infection. Measles infection caused elimination of 11–73% of antibodies in the children. Recovery of antibodies occurred after natural re-exposure to pathogens.

Reference: Science 2019;366(6465):599-606
Abstract

Incomplete genetic reconstitution of B cell pools contributes to prolonged immunosuppression after measles

Authors: Petrova V et al.

Summary: This *in vitro* study determined the immunological factors underlying the prolonged immune impairment seen after measles virus infection. Using B cell receptor sequencing of human peripheral blood lymphocytes before and after measles infection, two immunological consequences of measles were identified that persisted after the resolution of clinical disease. These were changes in the naïve B cell pool leading to immunological immaturity, and changes in memory B lymphocyte diversity.

Reference: Sci Immunol 2019; published online Nov 1
Abstract

Comment (HPH): While the potential complications of measles infections are well documented – encephalitis, pneumonia, ear infections and so on, measles virus infection also induces an immune amnesia. This leaves the patient immune suppressed. The virus destroys the hard-earned immune memory to other infections, maybe last year's cold, that terrible dose of flu, maybe that gastro that had you in bed for a week … or maybe even that immunity you developed to something truly vile that might kill you next time! Measles appears to replace some of your existing memory T cells and B cells with measles memory T cells (great for measles immunity!) but you are then left vulnerable to a host of other things. So, basically measles makes you weaker. Measles virus likes to infect cells of the immune system and it has a predilection for memory cells. Of course, one of the things the body does to fight a viral infection is to kill virally infected cells. The immune system is forced to attack itself in a bid to extinguish measles infection. That is on top of the virus making the cells explode as it disseminates further. This gives a hint as to why secondary infection is so common with measles, not just the damage to skin, respiratory and gastrointestinal tract but also your hard-earned immune memory. In 2015, big data highlighted massive declines in childhood disease after widespread measles vaccination. It showed that up to half of all childhood deaths from infectious diseases could be explained by non-measles infection that had been occurring because of measles infection. The effect lasted for a few years. While this has been suspected to be the case for over 100 years, it has now been empirically demonstrated. These two most recent studies reveal two important things. Firstly, B cells are affected and that includes naïve (future immunity), plasma (antibody secreting), and memory B cells. Secondly, up to 73% (11–73%) of the antibody repertoire was obliterated indicating some individuals are quite severely affected. This memory has to be reconstituted by re-exposure to the pathogens. In countries with good healthcare like NZ we aren't likely to see mortality associated with these additional infections, but sadly increased death is a consequence in low-resource settings.

Characterizing the impact of spatial clustering of susceptibility for measles elimination

Authors: Truelove S et al.

Summary: If susceptible individuals have preferential contact with one another, communities may remain vulnerable to measles epidemics even when vaccination coverage targets are met. This article discussed the impact of spatial clustering of susceptibility on the critical vaccination threshold necessary to prevent a measles epidemic. The investigators calculated that, after accounting for spatial clustering of susceptibility, the critical vaccination threshold was 96% and outbreak probability after a single introduction was 23%.

Comment (HPH): A major contributor to our recent epidemic has been immunity gaps in adolescents and younger adults aged 15–29 years. However, if we are unable to attain at least 95% coverage in our infant programme then we will probably find ourselves in a *déjà vu* situation. Not only is our coverage falling but we have about 88% of 5-year-olds full immunised – the target for two doses of measles vaccine is 95%. That might not sound too bad but the unvaccinated are not nice and evenly spread among the population. Risk factors for not being vaccinated are on one hand deprivation and access to services and on the other hand anti-vaccine and vaccine hesitant people; these communities tend to cluster together. The vaccine targets assume an even mixing across the population, however, this is not the reality. As countries approach 95% coverage and elimination, they must take the clustering of unimmunised people into account – when coverage is low it does not matter so much. One of the recommendations from this research is where coverage is overall high then the focus must shift to the clusters. Given that there are multiple reasons for non-immunisation, addressing this problem will require an active and multipronged attack. We can't just sit on our 92% laurels!

Reference: Vaccine 2019;37(5):732-41
Abstract

It's not all about autism: the emerging landscape of anti-vaccination sentiment on Facebook

Authors: Hoffman B et al.

Summary: This study evaluated the emerging landscape of anti-vaccination content on social media. 197 individuals (89% female) who posted anti-vaccination comments in response to a message promoting vaccination were analysed.

Comment (HPH): Eating yogurt cures human papillomavirus and there is no such thing as polio but pesticides cause the paralysis – not! But these are the kind of myths that social media outlets facilitate giving a false balance to the force. While it is likely that this kind of nonsense bounces around in echo chambers even a small influence can have significant downstream effects when it comes to maintaining vaccine confidence and uptake. While these kinds of crazy, and potentially dangerous, messages are only generated by a few individuals there is a much larger group of people that can be persuaded by them, even just enough to not make the vaccination appointment. A decade ago I complained about the false balance in the newspapers. Now I appreciate that even the lazier outlets tended to filter scientific information and do a little fact checking – come back all is forgiven! At least they usually gave a voice to an expert, even if it was less than we may have liked. Our old media model that once moderated the force has broken down, on social media no one knows whether you are a dog, a cat, or a bot. This year there were some moves by some platforms to minimise the exposure of anti-vaccine material. If you search Pinterest for vaccine-related topics, only links to reputable health organisations such as the WHO appear. We are still figuring out the boundaries as to what constitutes legitimate free speech and what oversteps a line. Personally, I think the generation and dissemination of misinformation along with trolling and harassment well and truly cross a line that is not in anyone's interest except those peddling woo. There is a growing polarisation between scientific information and fake news and people tend to gravitate to one or the other to exist in an echo chamber. This study concludes by recommending health professionals leverage social networks to deliver more effective, targeted messages to different constituencies. I could not agree more.

Reference: Vaccine 2019;37(16):2216-23
Abstract