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Virology

The Royal Australian and New Zealand College of Obstetricians and Gynaecologists

O&G Magazine

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Virology

11 Editorial: going viral
John Schibeci

13 Virology: a guide to the basics
Iain J Abbott and Amanda M Dennison

18 From viruses to vanguard vaccines: the development of vaccination
Lucy Weaver

22 The vaccine non-responder
David Speers

24 HIV infection in women
Sarah Martin, Alexandra Tyson and Frank Bowden

26 Facing Ebola in Sierra Leone
Cath Deacon

28 HPV vaccination program: the Australian experience
Ian Hammond

30 HPV vaccination in low- and middle-income countries
Heather Franklin

32 HPV testing explored and explained
Louise Farrell

34 Viral hepatitis in pregnancy
Dominic Ray-Chaudhuri

38 Viral gastroenteritis and hepatitis A in pregnancy
Stephen Robson and Kathryn Daveson

40 Influenza virus in pregnancy
Lucy K Somerville, Dominic E Dwyer and Jen Kok

44 Dengue in Australia: the key points
Helen M Faddy, Elvina Viennet, Robert LP Flower and William JH McBride

46 Parvovirus infection in pregnancy
Sylvia Ross and Audrey Long

48 Rubella and varicella in pregnancy
Caitlin Keighley, Zoe Jennings and Gwendolyn Gilbert

Letters to the editor

57 Aldo Vacca remembered
Joanne Ludlow

58 Honouring Aldo Vacca
Clare Boothroyd, Anthony Cerqui, Elizabeth McKenna, Eva Kretowicz and Julie Lindstrom

59 Aldo Vacca's legacy
Alec Welsh

Women's health

50 Sim one, do one, teach one: the past, present and future of simulation
Sarah Janssens and Erin Wilson

Case report

53 A heterotopic or secondary abdominal pregnancy?
Georgia Heathcote

54 Journal Club
Brett Daniels

55 *Q&A*: HPV and throat cancer
Min Karen Lo and Julian White

The College

5 From the President
Michael Permezel

60 Staff news

61 After the storm
Rufina Latu

64 RANZCOG Women's Health Award winners for 2014

64 Notice of deceased Fellows

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From the President

Prof Michael Permezel
President

It was very pleasing to see more than 2300 participants at the Joint RCOG/RANZCOG Event 2015, in Brisbane. Initial feedback has acclaimed the meeting as an outstanding success and many congratulations are owed to the principle organisers A/Prof Ted Weaver and Dr Clare Boothroyd. A full report on the Congress will run in the next issue of *O&G Magazine*, but some of the very many photos from the Congress are shown here to show the scale of the event.

There were many highlights of the meeting, including truly superb local and international keynote speakers. The all-encompassing message was we should have a strong evidence-base to clinical practice in women's health, but – importantly – the best evidence is not always a randomised controlled trial.

FIGO 2021 Congress

The International Federation of Gynecology and Obstetrics (FIGO) has recently revised the process of nominations so that bids to host the Congress are made by host cities rather than member societies. As such, Melbourne and Sydney are submitting bids to host the FIGO 2021 Congress, with the College supporting both. Each city was visited by representatives of FIGO in early March 2015, along with others in the Asia-Oceania region bidding to host this prestigious meeting. The delegation will make a recommendation to the FIGO Executive at its meeting in May, and the final decision will be voted on at the FIGO 2015 Congress in Vancouver.

FIGO 2015 Congress

College members will no doubt be aware that the 2015 FIGO World Congress is to be held in Vancouver, Canada, 4–9 October 2015. In 2014, the College applied to host a society session within the Congress program and confirmation of acceptance

A packed auditorium bears witness to the success of the Joint RCOG/RANZCOG Event.

Congress organisers, A/Prof Ted Weaver and Dr Clare Boothroyd, open the Joint Event.

has been recently received. Those attending the meeting in Vancouver are encouraged to attend the RANZCOG session on Monday, 5 October 2015, featuring presentations on perinatal mental health; lessons from practice in resource poor settings; and violence and other non-obstetric trauma in pregnancy.

Additionally, as part of the FIGO award program recognising women obstetrician gynaecologists, I am pleased to advise that Dr Mary Schramm is to receive this award at the 2015 FIGO World Congress for her immeasurable contribution over a 30-year period to the health of the women and babies of Fiji.

> 'Efforts to improve procedural training remain a key area of activity for the College...While it is easy to be critical without offering solutions, the College has determined a number of strategies to improve procedural training.'

Training

Efforts to improve procedural training remain a key area of activity for the College. All acknowledge the changes in quantity of training brought about by many influences, including safe working hours, reduced utilisation of overseas experience and an increasing recourse to medical management of conditions that had previously required surgery. While it is easy to be critical without offering solutions, the College has determined a number of strategies to improve procedural training.

One key strategy, among the many that have the College's focus, is the increased use of simulation. In March, the Council was very pleased to receive an excellent presentation from Dr Sarah Jansens and Dr Michael Beckman, Mater Health Services, with a

RANZCOG President Prof Michael Permezel addresses Congress delegates.

suggested plan for a structured introduction of simulation across all training sites (for an overview of the role for simulation in training see p50). As a first step, Trainees and training institutions will be surveyed to explore what is currently available to Trainees at the various training sites.

The e-portfolio continues to progress with electronic logging of all training procedures planned for the 2016 training year. It is envisaged that, with the availability of detailed information on the specific procedures, their complexity and the quantum available to Trainees at any given site, hospital allocation of Trainees will be adjusted to capitalise on the best-available training opportunities.

Basic skills

While completion of a Basic Surgical Skills Workshop has been a compulsory requirement for Year 1 FRANZCOG Trainees for a number of years, the Education Strategy Committee has also recently approved the introduction of a Basic Obstetric Skills Workshop for Trainees. While recognising the increasing competition for selection onto the FRANZCOG Training Program, women's health is no longer a core requirement of some medical school curricula and, as such, a need for early training in basic obstetric skills has been identified by the Committee and will be a compulsory requirement for Trainees commencing in the Training Program from 1 December 2016. This need has been balanced against the impost of requiring attendance by Trainees at yet another workshop.

FRANZCOG Training in resource-limited settings

The College recognises that placements in resource-limited settings can provide valuable training experience and the number of requests from Trainees wishing to undertake assignments in such settings continues to increase. As such, the Board has approved a guidelines document that outlines the steps and circumstances in which training in resource-limited settings might be credited towards Core or Advanced Training. Such training, if deemed suitable, could be approved as a substitute for the rural rotation for Trainees in the Core Training Program. The guidelines are available on the College website.

eLearning developments

The number of modules and resources that are available to Trainees

and Fellows on CLIMATE continues to grow. In addition to the core CLIMATE modules and activities that support the FRANZCOG and Diploma curricula, the eLearning platform hosts webcast presentations from previous ASMs; online lectures; landmark clinical trial papers; subspecialty resources; Regional Committee links; revision course presentations; modules for research, training supervisors and clinical educators; and a pregnancy and alcohol online course, to name a few. I encourage you to explore the resources available to you on CLIMATE. You will need to log in using your user name and password. If you need to be reminded of these, use the Lost Password link.

Women's health

The withdrawal of PGF2alpha by Pfizer from the Australian market has now proceeded. The College has been advised that pharmacies can readily obtain PGF2alpha manufactured overseas from pharmaceutical wholesalers using the Special Access Scheme Category A (life-saving medication).

Subscriptions

Fellow subscriptions will be unchanged, save for the necessary CPI increase. For the 2015–16 financial year, Fellows will retain the option of paying online, by post or using telephone banking. However, from 2016, the subscription will need to be renewed online, with an individual's practice profile updated as part of the process. While the College is reluctant to impose a compulsory survey on Fellows and appreciates the burden of an additional requirement, it is extremely difficult to plan training and educational programs without substantive and up-to-date knowledge of the current clinical profile of our Fellows. This will occur in a manner similar to that undertaken by the regulatory body at the time of renewing medical registration and will be pre-populated one year to the next; however, it will specifically address the practice of our specialty.

> 'The College recognises that... senior Fellows make major contributions in clinical teaching and administration in addition to their clinical work.'

Semi-retired Fellows

A Retired Fellow does not pay a subscription; however, the College recognises a number of Fellows reduce the size of their clinical practice as they approach retirement and find the subscription a major financial burden. The College recognises that these senior Fellows make major contributions in clinical teaching

Prof Ian Symonds holds the College mace at the presentation ceremony, flanked by members of the RANZCOG Board.

and administration in addition to their clinical work. Attempts to define semi-retired status by size of practice has proved difficult and the College has now made the Semi-retired Fellow membership category available to those who: are and have been actively practising as a Fellow of RANZCOG for at least 30 years and have an annual, pre-tax medical income of not more than AUD$60 000 (or the equivalent). Semi-retired Fellows pay half the annual subscription of a full Fellow and are required to submit an annual declaration regarding their eligibility for this membership category.

Selection

The FRANZCOG training selection process for New Zealand is well under way at the time of writing this report. The Australian process has also just commenced. Selection is an intensely competitive process, which must occur in a fair and transparent manner while striving to recruit the best-possible future specialists to our discipline.

A persistent issue with recent selection has been a recurring difficulty in translating current workplace performance into the selection score. There is widespread acceptance that the highly performing resident or unaccredited registrar is more likely to be a better Trainee and future specialist than the poor performer. Referee reports score almost all Trainees uniformly highly, regardless of what questions are posed or the scoring system used. In order to obtain meaningful hospital input into selecting the Trainees they will be asked to employ, the College will ask the hospitals to rank applicants for training who are working or have worked at their hospital. I urge all Fellows and Trainees to provide input into this process to ensure that the best-performing applicants are selected for entry into training in our specialty.

Social media

Timed to coincide with the Joint Congress, the College recently launched its Facebook page: www.facebook.com/ranzcog . RANZCOG will be regularly updating its page and entries and I encourage those who use Facebook to connect with the College through this medium.

Chief Executive Officer

The Board is very pleased to announce the appointment of Ms Alana Killen as the new CEO of RANZCOG. Alana comes to the College after approximately five years as CEO of the Australasian College of Emergency Medicine and is expected to commence at RANZCOG on 29 June 2015.

Editorial: going viral

Dr John Schibeci
DRANZCOG

'It's only a virus.' How often do those of us who are GPs utter these words in a typical day's work? The poor virus becomes the default, the fall guy when we don't know the diagnosis, but expect the patient to recover fully from their illness in a few days. Yet how many of us really understand the structure and function of viruses; how they exert their influence on the cell and the organism at large? Not many, perhaps. A quick random survey of my colleagues, registrars and medical students supports this assertion. They agree they know very little of such matters and were taught even less at an undergraduate level, especially in these days of case-based learning.

The word virus comes from the Latin for poison. The 1960 Nobel laureate and immunologist, Sir Peter Medawar, described the virus as 'a piece of bad news wrapped in a protein'. Not all viruses are bad news, however, many function within, and interact with, their hosts without causing damage. Interestingly, in his book Genome[1], Matt Ridley states that human endogenous retroviruses account for 1.3 per cent of the human genome. These have been incorporated into human DNA during its millenia of evolution. This is a more impressive fact when one notes that, at that time, proper genes were thought to only account for three per cent of our genome.

Why do viruses exist at all, one may ask? They are probably not even alive, certainly not in the sense that living tissue is. There is no doubt that they are population controllers; were it not for bacteriophages (bacterial viruses) our planet would have been overrun by bacteria. Viruses are fascinating: how they recognise their target cells, invade the cell, reproduce either in the nucleus or cytoplasm, reassemble and then egress from the cell in their tens to thousands to reinvade more cells could be the stuff of a story in a Boy's Own annual.

As doctors, we are mainly interested in viruses that cause disease and particularly, as obstetricians and gynaecologists, those which are relevant to our specialty. It is these viruses that are covered in this issue of *O&G Magazine*. Viruses that cause infection (HSV, influenza, parvovirus, hepatitis B and C, CMV, HIV, rubella, varicella, dengue fever and the ever-so-topical Ebola) and neoplasia (Hepatitis B, hepatitis C, HPV, HIV, EBV) can be read about here.

Vaccines and immunisation have been the mainstay of management or, more correctly, prevention of viral diseases since the late 18th century. In 1798, Dr Edward Jenner started immunising people against smallpox by deliberately infecting them with cowpox, more than 100 years before it was known viruses even existed. Tobacco mosaic disease was found to be caused by a sub-bacterial particle in 1893, by Martinus Beijerinck (who coined the term virus), but it was not until 1935 that Wendell Meredith Stanley successfully crystalised it. The discovery of viruses grew from then on, especially with the development of the electron microscope, and a steady production of antiviral vaccines ensued throughout last century and continues today. Vitally, this issue covers topics on immunisation against important obstetric and gynaecological-relevant viruses.

We hope you enjoy this issue of *O&G Magazine* and please don't think of it as forced learning because, when you really get into it, this micro-lilliputian world of virology is more interesting than you could have imagined.

Reference

1 Ridley M. Genome: The Autobiography of a Species in 23 Chapters. London: Harper Collins; 1999.

Virology: a guide to the basics

Dr Iain J Abbott
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Viruses are ultramicroscopic, metabolically inert infectious agents that replicate only within living cells. Viruses occur universally and affect every animal, plant and eukaryotic micro-organism on the planet and, although some viruses affect the health of their hosts, most have very little or no impact. Unlike every other domain of life, which has double-stranded DNA (dsDNA) as its genetic program, virus genomes may be composed of either DNA or RNA. The genetic material is then arranged as either double or single strands. Single-stranded RNA (ssRNA) viruses are then further classified as being either positive-sense or negative-sense with respect to the messenger-RNA coding strand. The virus genome can have a linear or circular arrangement and consist of a single or multiple segments. Compared with bacterial genomes, viral genomes are small, but can range over 100-fold in size (in other words, from 3000 nucleotides to 1 200 000 base pairs). Viral genomes are housed within a protein structure that forms the virus particle (see Figure 1). In some viruses, this nucleoprotein is surrounded by further protein or a lipid bilayer, referred to as the envelope. The outermost proteins of the virus particle allow the virus to recognise the correct host cells and gain entry into its cytoplasm. The simple composition of the virus structure means that it requires enzymes and other mechanisms from within the host cell in order to replicate. The survival of viruses is therefore dependant on the host species. A simplified classification of common DNA and RNA viruses affecting humans is presented in Tables 1 and 2.

Box 1. Diagnostic virology methods

- Cell culture
- Cytology
- Histopathology
- Electron microscopy
- Antigen detection
- Nucleic acid detection
- Serologic assays

Diagnostic virology

Laboratory techniques have advanced greatly in recent times, mainly with the advent of molecular methods. Different diagnostic laboratory methods are outlined in Box 1. Cultivation of viruses in cell culture can be extremely sensitive. One viable virion may be sufficient to initiate a positive result. Culture also has the potential to detect unsuspected, multiple or even novel viruses. Some of the shortcomings of this traditional method include: technical difficulty, expense, slow turnaround time, the requirement for different cell-lines for different viruses and

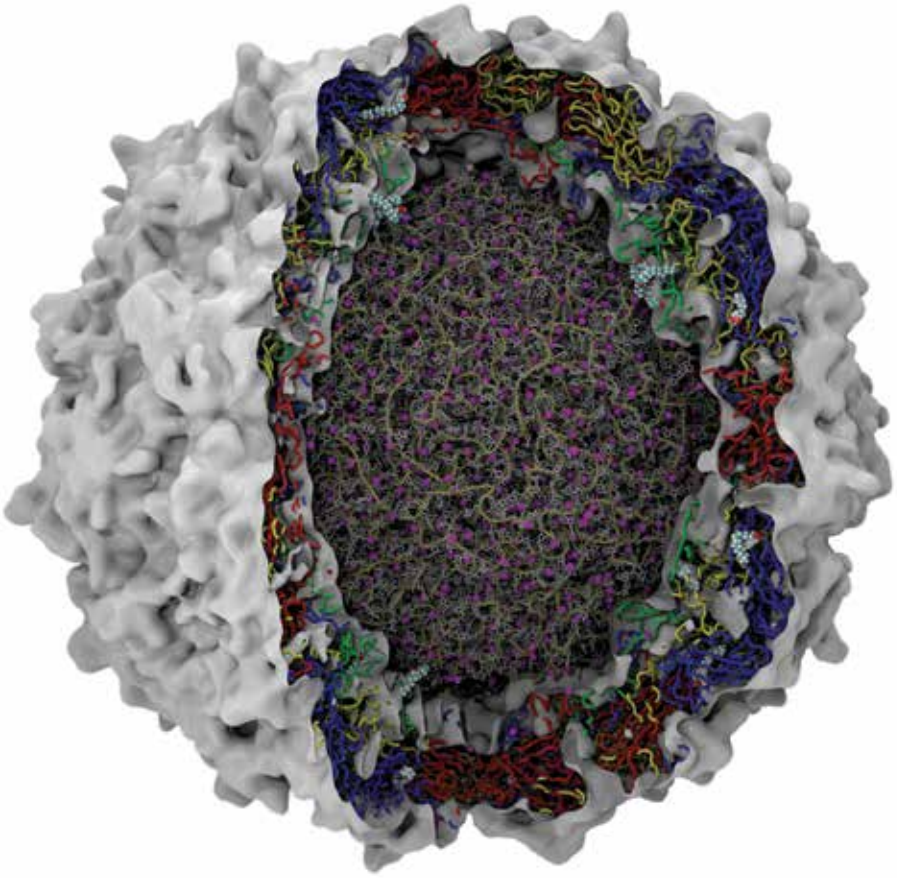

Figure 1. Schematic representation of a picornavirus virion. Cutaway representation of a complete picornavirus (poliovirus) virion. Image shows the genomic RNA in the core with associated Magnesium ions (purple). The protein chains that comprise the surrounding capsid are shown as Blue (VP1), Red (VP2), Yellow (VP3) and Green (VP4). Courtesy of Jason Roberts, National Enterovirus Reference Laboratory, Victorian Infectious Diseases Reference Laboratory, Melbourne, Australia.

Table 1. DNA viruses.

Genome composition		Replication site	Envelope	Family	Genus	Common species example
Double stranded	Linear	Cytoplasm	Y	*Poxviridae*	*Orthopoxvirus*	Variola, Vaccinia, Monkeypox viruses
					Molluscipoxvirus	Molluscum contagiosum virus
					Parapoxvirus	Orf virus
		Nucleus	N	*Adenoviridae*	*Mastadenovirus*	Human adenovirus A - G
			Y	*Herpesviridae*	*Simplexvirus*	Herpes simplex virus 1 + 2
					Varicellovirus	Varicella-Zoster virus
					Cytomegalovirus	Cytomegalovirus
					Roseolovirus	Human herpesvirus 6 + 7
					Lymphocryptovirus	Epstein-Barr virus
					Rhadinovirus	Human herpesvirus 8
	Circular		N	*Polyomaviridae*	*Polyomavirus*	BK virus, JC virus
				Papillomaviridae	*Alphapapillomavirus*	Human papillomavirus 32, 10, 61, 2, 26, 53, 18, 7, 16, 6, 34, 54, 90
					Betapapillomavirus	Human papillomavirus 5, 9, 49, 92, 96
					Gammapapillomavirus	Human papillomavirus 4, 48, 50, 60, 88, 101, 109, 112, 116, 121
					Mupapillomavirus	Human papillomavirus 1, 63
					Nupapillomavirus	Human papillomavirus 41
	Circular; Rev. transcribing		Y	*Hepadnaviridae*	*Orthohepadnavirus*	Hepatitis B virus
Single stranded	Linear		N	*Parvoviridae*	*Bocavirus*	Human bocavirus
					Erythrovirus	Human parvovirus B19

that a viable virus is required for successful culture. For these reasons, viral culture has been replaced as a first-line diagnostic technique by simpler, faster methods.

Cytology can provide important clues to the presence of viral infection, and generally implicates a group of viruses rather than a specific virus. Cytological examination can be performed on smears, on slides prepared by cytocentrifugation of fluids and on 'touch preps'. Tzank and Papanicolaou smears are examples of such techniques, which demonstrate the presence of HSV or VZV infection, or evidence of HPV infection, respectively. These are largely of historical interest only.

Histopathological findings suggestive of viral infection include intranuclear and intracytoplasmic inclusions, multinucleated giant cells and syncytia. Histopathology is enhanced by the use of immunohistochemistry to detect specific viral antigens and in-situ hybridisation to detect specific viral nucleic acids. This enhances the sensitivity and allows for identification of specific agents.

Electron microscopy (EM) provides a means to directly visualise the infecting virus and, like cell culture, allows for the identification of unsuspected, multiple or novel viruses. Many viruses have distinctive appearances under EM, which allows for identification to the family level, but this requires a skilled operator and dedicated and expensive equipment. Use of immunological techniques, such as immunogold labelling, can increase sensitivity somewhat and add a specific antigenic identification component to EM.

Antigen detection directly from clinical specimens can provide rapid information (within minutes to hours of specimen receipt) and is not dependent upon the presence of viable virus. The techniques most widely used are agglutination techniques, such as latex agglutination, fluorescent antibody (FA) staining, immunoperoxidase (IP) staining and enzyme immunoassay (EIA). These techniques are based on antibodies that specifically bind to the virus being sought. Although a versatile method, antigen detection is not as sensitive or as specific as nucleic acid amplification techniques and cannot be applied to all viruses, especially when the target virus has multiple serotypes and antigen variation.

Molecular methods have transformed the field of diagnostic virology. Viral nucleic acids, which are relatively stable to environmental conditions (DNA more so than RNA), can be detected regardless of the viability of the virus. Depending on the design of the primers and probes, amplification techniques, such as polymerase chain reaction (PCR), can either be very specific to a target (for example, the vaccine strain of measles virus) or target a genus or family for broader based detection (such as panflavivirus detection). This technology is now standard in most laboratories. Commercial assays continue to simplify that process and are potentially able to identify multiple different targets from the one specimen. Furthermore, assessment of viral load allows for the determination of disease burden and response to therapy. Sequencing the amplified nucleic acid product also allows for virus identification and further characterisation such as subtyping, assessment of genetic drift, relatedness between strains and the assessment of drug-resistance mutations (for example, HIV genotype).

Serology is the method of measuring an antibody response to an infection and remains a powerful tool in viral diagnostics. There are many different types of assays, although the most common are EIA (or similar) assays. EIAs are now commonly incorporated into automated systems. Neutralisation and Western blot assays, however, remain the gold standard in many instances. Serologic diagnosis is dependent on the kinetics of the antibody response to infection, with an initial IgM phase and then subsequent IgG. Placental transfer of IgG antibodies limits the use of IgG-based serological testing in the newborn up to the age of 12–18 months. Depending on the infecting virus, the relation between the clinical syndrome, the viral and antibody kinetics can be markedly variable. Serology may be unhelpful in the acute setting, requiring a convalescent bleed for diagnosis. Serological evidence of an acute infection can be made based on IgG seroconversion, where the initial

Table 2. RNA viruses

Genome composition		Replication site	Envelope	Family	Genus	Common species
Double stranded	Linear	Cytoplasm	N	*Reoviridae*	*Rotavirus*	Rotavirus A, B, C
Single stranded	Linear; Neg. sense	Nucleus	Y	*Orthomyxovirus*	*Influenzavirus A-C*	Influenza A, B & C viruses
		Cytoplasm		*Filoviridae*	*Ebolavirus*	Cote d'Ivorie, Sudan, Zaire ebolaviruses
					Marburgvirus	Lake Victoria marburgvirus
				Rhabdoviridae	*Lyssavirus*	Rabies & Australian bat lyssavirus
				Paramyxoviridae	*Henipavirus*	Hendra, Nipah viruses
					Morbillivirus	Measles virus
					Respirovirus	Human parainfluenza virus 1 + 3
					Rubulavirus	Human parainfluenza virus 2 + 4, Mumps virus
					Metapneumovirus	Human metapneumovirus
					Pneumovirus	Respiratory syncytial virus
	Linear; Ambisense			*Arenaviridae*	*Arenavirus*	Lymphocytic choriomeningitis virus
				Bunyaviridae	*Hantavirus*	Hantaan virus
					Nairovirus	Crimean-Congo haemorrhagic fever virus
	Circular; Neg. sense			*Deltavirus*	*Deltavirus*	Hepatitis delta virus
	Linear; Pos. sense			*Coronaviridae*	*Alphacoronavirus*	Human coronavirus 229E & NL63
					Betacoronavirus	Betacoronavirus 1, Human coronavirus HKU1, SARS & MERS-CoV
			N	*Caliciviridae*	*Norovirus*	Norwalk virus
					Sapovirus	Sapporo virus
				Hepeviridae	*Hepevirus*	Hepatitis E virus
				Picornaviridae	*Aphthovirus*	Foot-and-mouth disease virus
					Enterovirus	Enterovirus A-D (inc. coxsackie-, echo- & poliovirus), Rhinovirus A-C
					Hepatovirus	Hepatitis A virus
					Parechovirus	Human parechovirus
				Astroviridae	*Mamastrovirus*	Human astrovirus
			Y	*Togaviridae*	*Alphavirus*	Barmah Forest, Chikungunya, O'nyong-nyong, Ross River, Sindbis virus
					Rubivirus	Rubella virus
				Flaviviridae	*Flavivirus*	Dengue, Japanese encephalitis, Murray Valley encephalitis, Yellow fever, West Nile (Kunjin) viruses
					Hepacivirus	Hepatitis C virus
	Linear; Rev. transcribing			*Retroviridae*	*Deltaretrovirus*	Human T-lymphotrophic virus 1 + 2
					Lentivirus	Human immunodeficiency virus 1 + 2

bleed was negative and the convalescent bleed positive. A rising titre of a virus-specific antibody across two time periods can also suggest recent infection. The presence of virus-specific IgM antibodies in a single acute phase specimen can provide a rapid diagnosis in the correct clinical setting, but care should be taken given the possibility of false-positive results, either owing to cross-reacting antibodies or non-specific reactivity. The strength of IgG binding, known as IgG avidity, can also be used to assess the timing of an infection, where a low IgG avidity indicates a more recent infection (for example, CMV IgG avidity testing). Serology is also used for determining immunity (for example, hepatitis B virus, rubella virus and so forth).

Specimen collection and transport

The majority of errors occur in the pre-analytical phase of viral diagnostics. Beyond accurate labelling and safe and timely transport of the specimen, mistakes are often made either in the wrong test being ordered, an incorrectly collected specimen or a test requested at the wrong time relative to the clinical illness. Close liaison with the clinical microbiologist or infectious diseases service can often curtail these issues. Accurate and informative clinical notes will also enable the laboratory to best process, analyse and report the result accordingly.

Blood (whole blood, plasma or serum), urine, faeces, respiratory specimens, cerebrospinal fluid, biopsy tissue, ocular specimens, vesicles and other skin lesions, and amniotic fluid should be considered for diagnostic testing. PCR techniques can also be applied retrospectively to histopathology specimens, where paraffin-embedded tissue is finely shaved and processed prior to nucleic acid extraction. The presence of PCR inhibitors may, however, limit the diagnostic yield.

Diagnosis of viral infections with a short viraemic phase (for example, flavivirus infections) may rely on serology rather than molecular testing, depending on the timing of symptoms. In the setting of HIV infection, serology remains the standard testing algorithm. HIV RNA viral load assays, which are not licenced in Australia as diagnostic tests, however, may be used as

Box 2. Common viral causes of different clinical syndromes

- *Central nervous system infection**
  HSV, Enteroviruses, VZV, HHV6, arthropod-borne viruses, Influenza, HIV, LCM, Rabies
- *Respiratory tract infections#*
  Rhinovirus, Coronavirus, Adenovirus, Influenza virus, Parainfluenza virus, RSV, Human metapneumovirus, EBV
- *Gastrointestinal infections*
  Rotavirus, Norovirus, Astroviruses, enteric Adenoviruses
- *Skin and mucous membrane infections*
  HSV, VZV, enteroviruses, MCV, Orf virus, Papillomavirus
- *Genital tract infections*
  HSV, Papillomavirus, MCV
- *Viral hepatitis*
  Hepatitis A, B, C, D and E viruses, CMV, EBV, HIV, arthropod-borne viruses
- *Cardiac infections†*
  Enterovirus, Adenovirus, CMV, Influenza virus, Parainfluenza virus, Mumps virus, Parvovirus B19
- *Urinary tract infections*
  BK virus, Adenovirus, Hantavirus
- *Ocular infections*
  Adenovirus, Enterovirus, HSV, VZV, CMV, Influenza virus, Mumps virus, Measles virus
- *Childhood rash viral infections*
  Measles virus (First disease or Rubeola), Rubella virus (Third disease or German Mealses), Parvovirus B19 (Fifth disease or Erythema infectiosum), HHV6/7 (Sixth disease or Roseola infantum), VZV (chicken pox), Enterovirus
- *Congenital infections*
  CMV, VZV, HSV, Parvovirus B19, LCM virus, HIV, Rubella virus
- *Viral infections in immunocompromised patients*
  CMV, HSV, VZV, EBV (causing PTLD), HHV6, HHV8 (causing KS), Adenovirus, BK virus (causing haemorrhagic cystitis), JC virus (causing PML), Parvovirus B19, RSV, Enterovirus
- *Viral haemorrhagic fevers*
  Ebola virus, Marburg virus, Lassa fever virus, Yellow fever virus, Dengue virus, Hantavirus, CCHF virus
- *Blood-borne viruses*
  HIV, HTLV, Hepatitis B virus, Hepatitis C virus

**Includes meningitis and encephalitis; # includes upper and lower respiratory tract; † includes myocarditis and pericarditis.*
HSV, Herpes simplex virus; VZV, Varicella-Zoster virus; HHV6/7, Human Herpes virus 6 or 7; HIV, Human immunodeficiency virus; RSV, Respiratory Syncytial virus; EBV, Epstein-Barr virus; MCV, Molluscum contagiosum virus; CMV, Cytomegalovirus; LCM, Lymphocytic Choriomeningitis virus; PTLD, post transplant lymphoproliferative disorder; KS, Kaposi's sarcoma; PML, progressive multifocal leukoencephalopathy; CCHF, Crimean-Congo haemorrhagic fever virus; HTLV, Human T-lymphotrophic virus.

supplementary tests along with p24 antigen during the early phase of infection. In some clinical settings, a request for HIV pro-viral DNA is required and requires the collection of whole blood rather than plasma, to enable the collection and testing of the buffy coat (in other words, white blood cells).

Correct sampling is vitally important for the sensitivity of any test. Flocked swabs, for example, can capture the greatest amount of infected material for analysis. When a nose and throat swab is collected, the posterior aspect of the nasopharynx should be sampled, rather than anterior nasal cavity. Furthermore, when a lower respiratory tract infection is strongly suspected and an initial nose and throat swab is negative, then assessment of a deep respiratory sample (for example, broncheoalveolar lavage) should be considered before ruling out the diagnosis. Interestingly, some viruses – for example, measles virus – will continue to be shed in the urine for longer than from the blood or nasopharynx.

The timing of molecular testing for the investigation of in-utero infections is especially important, given sampling the amniotic fluid either too early in gestation or too soon after maternal exposure could result in a false negative result. In suspected CMV infection, for example, sampling of the amniotic fluid should wait until later than six weeks after primary maternal infection and ≥21 weeks gestation for optimal sensitivity.

Conclusions

Viruses can cause a wide variety of clinical presentations. Box 2 outlines the common viruses implicated in different clinical syndromes. The patient's vaccination history, predisposing immunocompromising conditions or medications, geographic location, seasonality and age are all contributing factors. Reactivation of latent infections may also contribute to morbidity and mortality, although this may be actively prevented by screening and providing appropriate prophylaxis (such as lamivudine or entecavir therapy to prevent hepatitis B reactivation). Box 3 outlines the common viruses encountered in the obstetrics and gynaecology setting. It should be noted that a positive diagnostic test does not necessarily infer clinical disease, especially in the setting of viruses that cause latent infection (for example, *Herpesviridae*), or when molecular detection represents dead virus, rather than viable disease-causing virus. Similarly, the inability to detect the virus does not rule out the diagnosis. The correct predisposing conditions, the current clinical presentation and the investigation results all need to be weighed up against each other.

Box 3. Important viruses for obstetrics and gynaecology

- Cytomegalovirus
- Enterovirus
- Hepatitis B
- Hepatitis C
- Human papillomavirus
- Herpes simplex virus
- Human immunodeficiency virus
- Influenza viruses
- Parvovirus B19
- Rubella virus
- Varicella-Zoster virus

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From viruses to vanguard vaccines: the development of vaccination

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Vaccination has been successfully implemented for the control of infectious diseases for more than 200 years. Since Edward Jenner (see Figure 1) first developed the smallpox vaccine in 1798, seminal work by many other scientists has led to the development of a number of different vaccines, targeted against various disease-causing viruses and bacteria. The success of immunisation cannot be denied: the mortality rate of diseases for which vaccines are available has decreased by more than 97 per cent and, in some cases, has led to the complete eradication of the disease (for example, smallpox, which was eradicated in 1980).[1]

Aligning with the adage 'prevention is better than cure', the basic premise behind vaccination is the controlled introduction of a non-infectious form of a target pathogen into the body, to allow development of specific immunity against the virus or bacterium, without causing a severe infection. While this process is relatively well understood by medical practitioners, the science behind how new vaccines are designed and developed into safe formulations may be less familiar. This article will explore how different viral vaccines are made and outline the complex journey involved in getting a new vaccine from the laboratory bench to the patient.

Viruses and the immune response

Viruses are incredibly small, highly infectious organisms that can only survive and replicate inside the living cells of a host organism (such as humans). The structure of a virus is relatively simple, typically consisting of two main entities: genetic material (either DNA or RNA) and a protective coating surrounding the genetic material, mainly consisting of proteins.[2] This protein shell contains a number of different and unique peptide segments, referred to as antigens, that the body uses to identify the virus. For example, in much the same way that humans generally distinguish each other through differences in hair and skin colours, the human body can identify and distinguish foreign organisms using these antigens.

Figure 1. Edward Jenner, whose pioneering observation that cowpox gave immunity to smallpox led to the science of vaccination.

Once a virus is inside a host cell, it can grow and proliferate at incredibly high speeds, hijacking cell after cell and rapidly causing an infection. Luckily for us, the body is programmed to respond to the presence of foreign pathogens quickly, via activation of the innate immune response.[2] This causes the release of various molecules, which attack the virus and helps to protect the body during the initial infection. Following this, the adaptive immune response is then activated. It consists of the cell-mediated (T-cell) and humoral (B-cell) immune responses that work in partnership to handle much of the dirty work that is involved during elimination of a virus from the host. A key event during the humoral immune response is the production of antibodies (immunoglobulins) that recognise and bind to the specific antigens of a virus, blocking the virus-host cell interactions or lysing virus-infected cells.[2,3] The production of memory B-cells is also activated during this response, which leads to long-lasting immunity and a faster initial immune response upon re-infection of the host with the same virus.

Table 1. A list of the different viral pathogens that humans can be immunised against, categorised according to their vaccine type.[5,8]

Vaccine type	Viral pathogen
Live, attenuated	Adenovirus Influenza (nasal spray) Measles Mumps Poliovirus (OPV) Rotavirus Rubella Smallpox Varicella (chickenpox) Yellow fever Zoster (shingles)
Whole inactivated/ killed	Hepatitis A Influenza (injection) Japanese encephalitis Poliovirus (IPV) Rabies
Recombinant/ purified subunit	Hepatitis B Human papillomavirus Influenza (injection)

Isolate, inactivate, inject

To give the body a head start in developing immunity against these viruses, early development of vaccines was focused on Louis Pasteur's principles of 'isolate, inactivate, inject' the causative organism.[1,4] In a nutshell, this involved isolating mutated strains or inducing a mutation in the virulent (wild-type) form of the virus to generate a strain with reduced or eliminated ability to replicate within the host. Termed 'live, attenuated' (see Table 1), these vaccines are highly effective at eliciting an immune response in the body, as they imitate the native, non-attenuated virus in nearly every way.[2,3] Some examples of these vaccines include chickenpox, shingles and yellow fever.

A second reason why many of these live, attenuated viruses make particularly effective vaccines is because the antigens produced by the virus do not change very much, meaning that humans can be immunised for life against many of these pathogens. One risk associated with these vaccines though is spontaneous reversion of the attenuated strain of the virus back to the wild-type, potentially causing disease in patients who have received the vaccine. Many cases of reversion have been reported for the oral poliovirus vaccine (OPV) that immunises humans against all three poliovirus types. Thus, given its associated risks, a different poliovirus vaccine – the inactivated poliovirus vaccine (IPV) – was developed and is now used preferentially to immunise against poliovirus, even though its protective action is not as good as OPV.[1,5]

In light of the above example, a second class of vaccines was developed for those pathogens where immunising with the attenuated virus is not feasible or not possible.[6] Therefore, rather than attenuating the virus to make it less virulent, some viruses are wholly inactivated or killed to make the vaccine. This is usually achieved by treating the live organism with chemical agents, such as formaldehyde, which renders the virus unable to penetrate cells or replicate in vivo.[6] As a result of this, whole inactivated or killed vaccines are generally less immunogenic than live, attenuated vaccines owing to their inherent loss of function. For this reason, a compound called an adjuvant is usually added to the vaccine formulation to help stimulate the immune system and promote longer lasting immunity. Adjuvants are typically aluminium salts or oil-in-water emulsions that help to increase or modulate the immune response.[7] Some examples of whole inactivated or killed vaccines are those for hepatitis A and Japanese encephalitis.[2,8]

In addition to inactivating or killing the virus, a third method for making vaccines involves isolating the purified protein of the virus shell, thus eliminating the viral genetic material from the vaccine formulation. This 'recombinant' process has been successfully implemented for the preparation of the hepatitis B vaccine.[2,8] Briefly, the basic laboratory process involves inserting the genetic code for the hepatitis B surface antigen HBsAg into yeast cells, which are then grown, before the protein is isolated from the cells, purified and formulated into the vaccine.[4]

New tricks, new vaccines

More recently, new methodologies have been developed for vaccine production against pathogens exhibiting high antigenic variability, such as the human papillomavirus (HPV). HPV has more than 170 different strains, many of them causing diseases such as cervical and oropharyngeal cancers, and genital warts.[9] Therefore, in order to be broadly protective, any HPV vaccine must incorporate many of these strains. Early development of the HPV vaccine began via expression and purification of the individual proteins (L1 and L2) of the virus shell of a cancer-causing HPV strain (HPV16) in an attempt to replicate the outer shell of the native virus.[10,11] While these proteins could be grown from cells in the lab, it was only under the right conditions that the L1 and L2 proteins self-assembled to form virus-like particles (VLPs) that mimicked the native shell of the virus. In this seminal work led by Prof Ian Frazer and Dr Jian Zhou, this procedure turned out to be the key trick in the development of the human papillomavirus vaccine as it then allowed for the preparation of a number of VLPs for many of the different HPV strains.[10,11] Thus, incorporating four different VLPs from the HPV types 6, 11, 16 and 18, the quadrivalent HPV vaccine Gardasil (Merck) now confers protection against the HPV strains that are responsible for 70 per cent of cervical cancers in women and 90 per cent of genital warts cases.

Trepidation and trials

While the discovery and initial development phase of a vaccine can take many years, the process involved in taking a vaccine from the bench to the patient is very lengthy and costly. During the discovery phase of a vaccine, laboratory and animal tests are conducted as the recommended pre-clinical trials. If the vaccine passes all of these tests, it then enters into the various phases for testing on humans, as shown in Table 2. Given the rigorous nature of these tests, many vaccine candidates often fail in either Phase I or Phase II trials. If a vaccine candidate is deemed efficacious and safe, what then follows is the approval and licensure of the vaccine, after which it is then made publicly available.[12] The time that this whole process takes does vary depending on each vaccine, however to give an example – in the most recent case of the HPV vaccine, the process from making the first HPV16 virus-like particle in the laboratory to the first licensed human immunisation took a total of 14 years.[12]

Vanguard vaccine development

While we can celebrate past successes in the realm of vaccination, we must also look forward to the development of new vaccines against a number of different disease-causing viruses for which no preventative treatment exists, including human immunodeficiency virus (see Figure 2), ebola and malaria.[4] Thankfully, science is providing important steps towards the development of new vaccines using a few different approaches. At the forefront of these technologies is 'reverse vaccinology', a process that involves sequencing the genome of a particular pathogen to identify antigenic sequences that can be used in the development of new vaccines. The key benefit of this process is that the vaccine is targeted only towards the antigens of

Table 2. The different phases of clinical trials required for approval to license vaccines.[12]

Clinical trial stage	Number of subjects tested	Tests conducted
Phase I	<100	Safety Immunogenicity
Phase II	>100–1000	Safety Immunogenicity Dosing Scheduling Method of delivery
Phase III	1000 to >10 000	Safety Efficacy

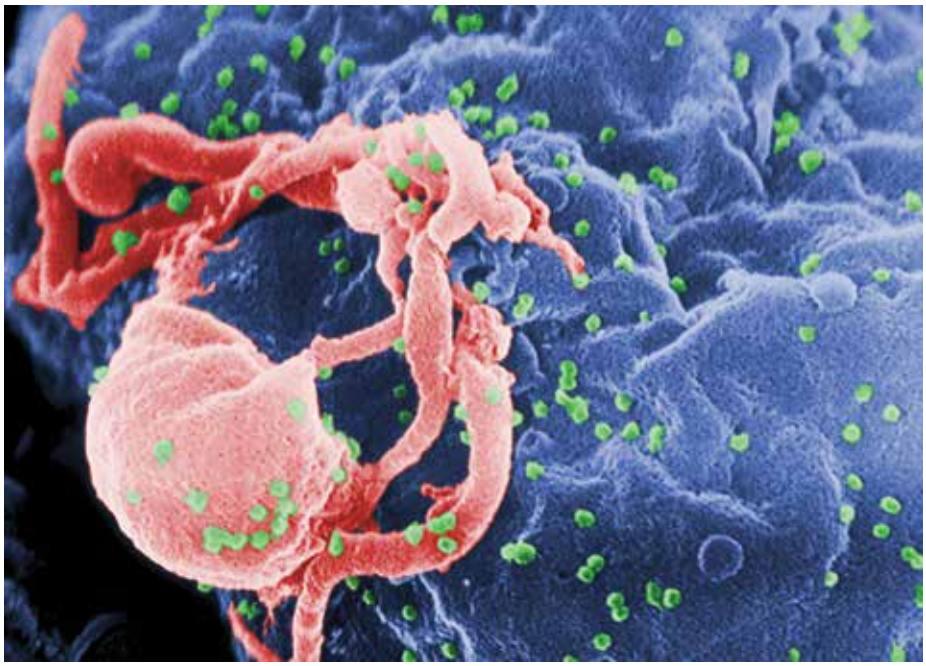

Figure 2. Scanning electron micrograph of HIV-1 budding (in green) from cultured lymphocyte. This image has been coloured to highlight important features. Multiple round bumps on cell surface represent sites of assembly and budding of virions.

interest and therefore the immune response is highly specific towards the target virus.[13]

Structural vaccinology is another technology that is being used for vaccine development against viruses with high antigenic variability. Briefly, this process looks more closely at the structure and prominence of different antigenic sequences within a viral protein and uses this information to guide the engineering of a new vaccine candidate, particularly when key antigens are obscured from the body's immune system.[4] Other methods of developing vaccines include instructive immunotherapy or programming of the immune system; and use of 'nano-carriers' for antigen delivery, such as liposomes, nanoparticles and dendrimers.[4,14]

While there are still a number of disease-causing pathogens with high rates of morbidity and mortality; the past 200 years of vaccine development has provided many success stories that we can be proud of. In particular, the pioneering work of Prof Ian Frazer and Dr Jian Zhou on the development of the virus-like particle and subsequent HPV vaccine is a recent example. In light of this, we can be confident that in the future many of these viruses will be outsmarted by next generation vaccines currently sitting at the forefront scientific investigation.

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The vaccine non-responder

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Vaccines stimulate the immune system to produce a protective immune response that mimics the response to natural infection; a process known as active immunisation. The protection induced by vaccines may involve cell-mediated immunity in addition to antibody responses. Therefore, despite the fact that antibody levels induced by vaccination tend to be lower than those produced by natural infection and may decline over time, long-lived protection may still be provided. The different types of vaccines (live attenuated, whole cell killed, protein or polysaccharide subunit) immunise to varying degrees by inducing B-lymphocytes, with some also generating cellular immunity. This is why some vaccines require boosters to provide ongoing or longer durations of protection. For example, vaccines containing polysaccharide antigen offer shorter lived protection than vaccines containing protein, because the immune response does not involve the T-lymphocytes needed for long-term immune memory.

Why do some people fail to respond?

Some individuals experience symptomatic or asymptomatic infection despite previous immunisation. Infection after immunisation can be owing to vaccine factors, resulting in inadequate antigenic stimulation, or host factors, owing to an inadequate immune response to an adequate antigen challenge. In Australia, where high-quality vaccines are available, vaccine failure is unlikely to be owing to a manufacturing fault, but may be owing to expiry of the shelf-life, inadequate cold chain maintenance during transport and storage or incorrect vaccination technique.

Primary and secondary host factors may lead to vaccine failure. In primary vaccine failure the patient fails to develop an immune response to the vaccination. The causes include host immune factors, such as immunosuppressive therapies and recognised immune deficiency illnesses, but can occur in a small proportion of otherwise immunocompetent individuals. Those who have recently received antibody-containing blood products, such as immunoglobulin or blood transfusion, may have an impaired vaccine immune response. Likewise, persistence of passively acquired maternal antibody may attenuate the immune response in infants.

Secondary vaccine failure is where the patient develops an initial immune response, but when subsequently challenged with natural infection the protective response is inadequate to prevent disease. Secondary vaccine failure is more likely with certain vaccines, owing to the type of immune response generated. The post-vaccination immune response may wane over time, especially if boosting from exposure to natural infection does not occur, so that the longer the duration since vaccination the more likely is secondary vaccine failure. Infection following secondary vaccine failure usually has fewer and less severe symptoms compared to infection in unvaccinated individuals.

Rubella

Rubella causes a self-limiting illness in children and adults, but is associated with a high risk of multiple congenital abnormalities if acquired in the first 12 weeks of pregnancy. After the first trimester, the frequency and severity of fetal damage following maternal infection decreases significantly and is rare after the 16th week of pregnancy, although hearing deficit may occur up to the 20th week.

Serological testing for immunity

Serological testing for immunity to rubella after routine measles-mumps-rubella (MMR) vaccination of children is not recommended. However, it is important to ensure that women of child-bearing age are immune to rubella. Women should be screened for rubella antibodies shortly before every pregnancy, irrespective of a previous positive rubella antibody result. Pregnant women who are not immune to rubella should be advised to avoid contact with any person who has confirmed or suspected rubella for six weeks from onset of their disease.

Rubella IgG levels >10IU/mL are usually considered protective against infection, but women with low antibody levels (IgG 10–20IU/mL) may rarely develop rubella reinfection if exposed, but with minimal (less than five per cent) risk of fetal damage. Also, the low rubella antibody level is likely to wane further to non-protective levels before a next pregnancy. Therefore, women with rubella antibody levels of 10–20IU/mL should be offered MMR vaccination following birth. MMR vaccine

Summary
In Australia, vaccination failure is more often owing to failure to vaccinate rather than vaccine failure. Primary vaccine failure can be owing to several causes, but does not usually indicate broader immunodeficiency. Secondary vaccine failure is most often owing to waning immunity over time. If booster vaccination for rubella and hepatitis B in those with inadequate antibody levels does not result in recognised protective antibody levels, then avoidance of those with possible rubella infection and use of HBIG following at-risk exposures, respectively, is recommended.

is contraindicated in pregnant women and pregnancy should be avoided for 28 days after vaccination, but breastfeeding is not a contraindication. Testing for rubella seroconversion eight weeks following MMR vaccination is recommended.

Lack of immunity following MMR

Some women will fail to develop protective rubella IgG levels following MMR vaccination. If they have only received one dose of MMR, the dose should be repeated and repeat serological testing performed eight weeks after administration. If, after having received another dose of MMR, the rubella IgG is still inadequate the woman should be managed as if she is non-immune as it is unlikely further vaccinations will help. Management advice for subsequent pregnancies includes ensuring all close contacts are rubella immune, minimising contact with people suffering a rash illness and investigating episodes of contact with rash illness or rubella-compatible illness in the mother. Serology (rubella IgM and IgG) and virus detection by rubella PCR may be helpful.

Hepatitis B

Hepatitis B prevalence is variable between countries and between ethnic groups within countries. Those infected at birth or as very young children most often become life-long hepatitis B carriers, the majority of which will be asymptomatic as young adults. Most newborns of hepatitis B surface antigen (HBsAg)-positive mothers can be protected by giving hepatitis B specific immunoglobulin (HBIG) and vaccine immediately after birth. Routine antenatal screening of pregnant women for HBsAg is therefore recommended to identify asymptomatic HBsAg-positive mothers. The risk of hepatitis B transmission from HBsAg-positive mothers to their newborns is dependent on the mother's hepatitis B DNA viral load at the time of birth, with vertical transmission occurring in a proportion of mothers with very high viral loads, despite giving HBIG and vaccine to the newborn.

Hepatitis B vaccine is not routinely recommended for pregnant or breastfeeding women, but neither pregnancy nor breastfeeding is a contraindication. In contrast, hepatitis B vaccine is recommended for all newborn infants. The first hepatitis B vaccine should ideally be given within 24 hours of birth with three subsequent doses at two, four and six months of age. This regimen results in seroconversion rates of more than 90 per cent in neonates, even with concurrent administration of HBIG. Low-birthweight preterm newborn infants do not respond as well to vaccines as full-term infants, therefore a booster at 12 months of age may be required. Vaccination alone within seven days from birth is reasonably effective in preventing infection from either an HBsAg-positive mother or other close contact with chronic hepatitis B infection.

Booster doses

Booster doses of hepatitis B vaccine (after completion of a primary course) are not routinely recommended for immunocompetent children and adults because there is good evidence that a primary course of hepatitis B vaccination provides long-lasting protection, even though vaccine-induced antibody levels may become undetectable.

Serological testing after vaccination

Post-vaccination serological testing is recommended four to eight weeks after completion of the primary course for children and mothers in close contact with HBsAg-positive individuals and healthcare workers. Anti-HBs antibody and HBsAg levels can be measured in infants born to HBsAg-positive mothers after nine months of age to avoid detection of anti-HBs antibodies from HBIG given at birth. If anti-HBs antibody levels are adequate (≥10mIU/mL) and HBsAg is negative, then the infant is considered to be protected.

Non-responders to vaccination

For non-responders (a person who has failed to develop protective antibodies despite a primary course of hepatitis B vaccine), the possibility of current hepatitis B infection should be investigated by testing for HBsAg and anti-HBc antibodies. If there are no markers of hepatitis B infection, the individual should be offered a single booster dose of vaccine and have anti-HBs antibody checked four weeks later. Individuals who are non-responders to the booster dose should have two further doses of hepatitis B vaccine at monthly intervals, and be re-tested for anti-HBs antibody levels at least four weeks after the last dose. If the anti-HBs level remains <10mIU/mL, the person is a non-responder to vaccination.

Healthcare workers and others at ongoing risk who were not tested for anti-HBs antibody within four to eight weeks after completion of the primary course can undergo serological testing for immunity. If they have an anti-HBs antibody level of <10mIU/mL, they can be given a single booster dose of vaccine as above. Individuals with immune memory from previous vaccination should respond to this booster dose. If the anti-HBs antibody level remains <10mIU/mL, the person should be managed as a non-responder to primary vaccination.

Persistent non-responders may not be protected against hepatitis B and should be informed about the need for HBIG following exposure to hepatitis B. There is no consistent evidence to recommend higher dose regimens, but some individuals may respond to intradermal vaccine, if locally available.

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HIV infection in women

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When the HIV epidemic was at its peak, in the 1980s, it was widely held to be principally a disease of gay men. In the US, Europe and Australia little attention was paid to HIV infection in women. When the true nature of the global epidemic was elucidated in the 1990s, it became apparent that heterosexual sex was the principal means of transmission of HIV in the developing world. Today it is estimated that 35 million people are infected worldwide and half of these are women.

Approximately 27 000 people live with HIV in Australia, of whom some 3500 (13 per cent) are women, a proportion that has remained stable for many years.[1] HIV diagnoses have been slowly increasing since 1996, and in 2013 there were 1236 new diagnoses in Australia, of which 161 occurred in women. Most of the transmission to women is through heterosexual contact, most usually associated with a partner from a country with known high prevalence of HIV, and only four per cent occurring from a known bisexual partner. Injecting drug use remains a rare form of HIV transmission. HIV rates are extremely low among female sex workers. Transmission from an infected woman to a female sexual partner is extremely rare, and has not been reported in Australia.[2] However, risk factors for HIV are not always easily discernible, a principle that underlies current Australian guidelines advising HIV testing as a routine part of antenatal care for all women.[3]

HIV damages the immune system mainly by its effect on CD4 cells. These lymphocytes are responsible for the co-ordination of the immune response, in particular in regard to opportunistic, fungal and viral infections. CD4 deficiency also predisposes the infected patient to a number of malignancies, especially non-Hodgkin lymphoma and Kaposi's sarcoma. In addition, HIV has direct effects upon the brain and lymphoid tissue of the gut.

Despite a number of promising candidates, there is still no effective vaccine against HIV, so prevention of infection remains the mainstay of the public health message. An HIV-infected woman poses a risk of transmission to her sexual partner and to her child. Both risks are significantly reduced, but not completely eliminated, by the use of antiretroviral drugs that lead to an undetectable viral load. Affordable antiretrovirals are now available in the developing world and it is estimated that 67 per cent of HIV-positive pregnant women in low- and middle-income countries received them to prevent transmission to their babies in 2013.[4]

Obstetrics and gynaecology concerns

While the numbers of HIV-positive women in Australia remain relatively low, HIV infection in the community is of relevance to obstetricians and gynaecologists, especially because of the risk of mother-to-child transmission pre-, intra- and postpartum. Furthermore, there are a number of reproductive health issues that affect HIV-infected women that need to be considered.

Increasing numbers of men and women living with HIV are choosing to have children. Between 2004 and 2013, 372 babies were born to women with HIV infection in Australia. Thirteen of these babies have perinatally acquired HIV infection; in over half of these cases, the woman was diagnosed with HIV after the birth of the child.[1] Routine antenatal screening for HIV allows successful intervention, which virtually eliminates perinatal transmission. With appropriate management, the chance of HIV transmission to a baby born to a mother who has HIV is less than 0.5 per cent.[5]

In the absence of Australian national guidelines for the care of HIV in pregnancy, it is possible to draw on US and UK guidelines, although there are some differences between the two that need consideration when devising local guidelines for multidisciplinary care.[6,7,8] Prevention of mother-to-child transmission includes antiretroviral treatment for the mother. In known HIV infection, treatment is usually commenced before conception, but should otherwise be started as early as possible after diagnosis of HIV in pregnancy, with the aim of maintaining an undetectable viral load. Maternal and fetal well-being are the most important considerations in determining the mode of delivery. Caesarean section offers no further reduction in transmission risk over vaginal delivery if the viral load of the mother is undetectable. However, if viral control has not been achieved, caesarean section is advised. Intrapartum instrumentation and invasive monitoring should be avoided. The newborn is also given a course of antiretrovirals for four weeks and should be exclusively bottle-fed.

Condoms remain integral to prevention of transmission of infection, unless conception is desired. Contraception for HIV-positive women is complicated by interactions between the combined oral contraceptive pill and HIV medications, and additional measures are usually recommended. Hormonal and copper intrauterine devices are considered to be safe and effective, but depo-medroxyprogesterone acetate has been implicated in increasing the risk of HIV transmission and is not usually a contraceptive of choice if acceptable alternatives are readily available.[9]

Human papillomavirus (HPV) immune surveillance may be impaired in HIV-infected women and the risk of cervical cancer is increased. Women with HIV tend to have higher rates of abnormalities on Pap smears and, despite advances in HIV treatment over the last decade, an annual Pap smear is still advised, rather than two-yearly as is generally recommended.[10]

HIV infection is associated with increased rates of premature menopause (less than 40 years of age). Early loss of ovarian function and childbearing capacity occurs in about seven per cent of infected women compared to less than one per cent women without HIV. Early menopause (between 40 and 44 years) is also more common, again affecting about seven per cent of women with HIV.[9] At present, there are no published data on the safety and efficacy of hormone replacement therapy in relation to menopause symptoms, cardiovascular risk and bone health for women living with HIV, which complicates informed decision-making.[11]

Living with HIV

Extraordinary advances have been made in HIV treatment. In 1990, the disease was essentially a death sentence and everyone who was infected was expected to die. Long-term survival was recognised, but rare. When combination antiretroviral therapy became widely available, in 1996, it was soon shown that CD4 decline could be halted and reversed, even in advanced disease. By 2005, most patients could be managed with a three-drug, single-tablet daily regimen. Life-long therapy is required, however; as the virus quickly reappears in the circulation on cessation of treatment. There are no major differences in the clinical course of HIV in men and women and recommendations for the timing and type of treatment are identical, except during pregnancy. Women with HIV treated with antivirals can now expect a close to normal life expectancy.[12]

More recently, the concept of 'treatment as prevention' has been promoted. Patients with early infection are highly infectious and so it is argued that the sooner they start treatment, the lower the risk of transmission to their partners. This intervention may reduce the number of new infections and lessen the overall risk of transmission at a population level. Pre-exposure prophylaxis is another recent facet of HIV prevention, whereby an individual at high risk of HIV infection takes a two-drug antiretroviral tablet daily to reduce their risk of HIV acquisition. Adherence is essential and, at present, cost prohibits widespread uptake of this approach.

Despite these dramatic advances in care and life expectancy, isolation and fear of disclosure of status are common aspects of many individual stories of living with HIV. Women who are parents face additional tough decisions about if, when and how to tell their children and uncertainty about the consequences for their family should their status become known.[13]

Conclusion

Women living with HIV in Australia are a minority within a minority, which poses particular challenges for women and their service providers. The strong and understandable desire for privacy in relation to an HIV diagnosis can reduce women's confidence in accessing services. Women may need to travel long distances to specialist centres to receive care, especially in relation to pregnancy. Nevertheless, the outlook for HIV-infected women and their children is excellent if they receive appropriate care and treatment. Obstetricians and gynaecologists have an important role to play in this regard.

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Facing Ebola in Sierra Leone

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Over a year ago, on 22 March 2014, the World Health Organization (WHO) declared there was an outbreak of Zaire ebolavirus in Guinea. In May 2014, cases were being diagnosed in Guinea, Liberia and Sierra Leone.[1,4] By early April 2015, a little over a year since the epidemic was declared, there had been more than 25 000 confirmed, suspected and probable cases in West Africa and more than 10 000 deaths. Sierra Leone alone had had more than 3800 deaths.[2]

The response required to ultimately control the epidemic involved the co-operation of local governments and organisations and international actors. An integrated approach was needed, which included ambulance services, expanded laboratory capacity, burial teams, health surveillance, contact tracing, health promotion and treatment beds.

One element of the international response in Sierra Leone involved constructing additional Ebola Treatment Centres (ETCs), a number of which opened in December 2014. This included Hastings Airfield ETC, just outside of Freetown, which is managed by Aspen Medical as part of Australia's Ebola response.[6]

Finally, in December, seven months after the first reported case, the ratio of beds to patients in Sierra Leone increased to above one. This was in part owing to the increased number of ETCs, but also to other measures starting to slow the epidemic.[7] Importantly, in most areas patients were now able to be cared for outside of their families, decreasing onward transmission.

Behavioural change was essential to control the epidemic. The riskiest behaviours included attending traditional funerals, caring for the sick at home and treatment of infected patients by health workers with inappropriate personal protective equipment (PPE) or training in the use of PPE.[10]

Traditional funerals are particularly dangerous as people travel widely to attend. The body is washed, and the mourners will touch and kiss the body before eating a communal meal. Funerals for pregnant women may pose extra risks as in many areas in West Africa it is taboo for the body to be buried unless the fetus is removed first.[11]

In Monrovia, the government made it compulsory for bodies to be cremated, despite it not being culturally acceptable. Médecins Sans Frontières (MSF), through necessity, suddenly found itself in the crematorium-building business.

Traditional burials were criminalised throughout West Africa, but the cultural sensitivities surrounding death led to reports of people hiding sick people and bodies and also to rumours of the harvesting of body parts. In Liberia, while working with MSF in Lofa district, I met one man who was frightened the burial team was planning to take his father's organs. Owing to these types of misconception, MSF in Lofa routinely offered relatives the opportunity to dress in PPE to witness the preparation of the body for burial.

Healthcare became a dangerous activity. It was estimated at one point that healthcare workers were 100 times more likely to catch Ebola than the general population and early in the epidemic they made up ten per cent of cases. Before the epidemic in Sierra Leone there were 0.2 doctors per 10 000 head of population, compared to 33 per 10 000 in Australia.[13,14] By 1 April there had been approximately 861 healthcare worker infections and 495 deaths in Guinea, Liberia and Sierra Leone.[3] Sierra Leone alone had lost 12 doctors to Ebola by the beginning of April, a serious loss to the healthcare system.

Some hospitals were forced to close as staff became infected. Many regional health centres, where the majority of the population receives their healthcare, were also forced to close as health workers either sickened or fled. Health centres and hospitals became associated with Ebola in the population's mind. Those that I visited that remained open were largely empty. Many patients sought healthcare at pharmacies, where it is common practice for pharmacists to administer intravenous fluids. This led to the infection of a number of pharmacists.[12]

Impact on women

Sierra Leone has a population of approximately 6.4 million, with a median age of 19. Life expectancy in 2012 was 45.3 with an infant mortality of 117 per 10 000 and maternal mortality of 890 per 10 0000 (2010).[15]

The situation for pregnant women worsened, largely because of disruption of access to health services rather than Ebola infection itself. The United Nations Population Fund estimated that the maternal mortality rate in Sierra Leone risked approaching 2000 per 10 0000 births, reversing all the improvements since the civil war and making Sierra Leone the most dangerous country in the world in which to be pregnant.[17]

Access to antenatal care and assistance with normal deliveries became limited owing to the closure of health centres and restrictions on travel.[18] The government also temporarily banned traditional birth attendants from working. Interestingly, female genital mutilation (FGM), which had had a prevalence of 89.6 per cent, was also banned.[3]

Women who did reach a hospital with antenatal or postpartum haemorrhage or abortion were likely to be turned away owing to the apprehension that they were presenting with Ebola. This is not surprising as the case definition of Ebola includes pregnant women with vaginal bleeding and a fever, or history of fever – a not uncommon presentation in obstetrics. Many hospitals stopped performing caesareans after doctors performing them became infected. Sadly, many midwives contracted Ebola attending what they thought were normal deliveries. Midwives were three to four times more likely to become infected than other healthcare workers.[18]

Ebola in pregnancy

The highest levels of virus are found in

blood, amniotic fluid, stool and vomit. Smaller amounts are found in saliva, sweat, breastmilk and semen. It remains unclear as to whether exposure to semen, breastmilk or sweat have actually resulted in infections although all body fluids are treated as if they are infectious.[9]

The high viral load in blood, placental tissue and amniotic fluid makes the management of pregnancy difficult and dangerous. Having to wear full PPE is an added problem, making interventions involving monitoring, such as the use of oxytocin for induction, largely impracticable.

Pregnant women who contract Ebola have a high mortality rate. One study in a previous epidemic estimated the case fatality rate to be 93 per cent.[19] It is unknown what the mortality rate is for the current epidemic, although MSF has had a number of survivors so it is hoped the mortality rate will be found to be better than 93 per cent. The vast majority of pregnancies end in miscarriage or fetal death in utero. For the rare live birth, neonatal mortality has thus far been 100 per cent. It is unknown how much of this is owing to transplacental transmission or infection during the delivery. It is assumed that any live-born baby is infected, although sample sizes are still very small.[20] This combination of poor outcomes for both pregnant women and infants makes management of these cases very stressful for the entire team. Women who miscarry or deliver during the acute phase of their illness frequently suffer from coagulation disorders and have a very poor prognosis.

A minority of women do survive the acute illness, testing negative for Ebola on blood PCR. However, where amniotic fluid has been tested when there has been an ongoing pregnancy, it has been found to be strongly positive for Ebola. In one case, reported by MSF, a woman delivered a macerated fetus 32 days after she had tested negative; the placenta and cord blood were still positive on PCR.[20,21]

In January 2015, in response to the challenges of dealing with obstetric cases, MSF opened a specialised obstetric unit outside of Freetown for women with suspected or confirmed Ebola, the first of its kind in the world. Based on their experience both in this and previous epidemics, MSF released a guideline in late 2014: Guidance paper Ebola Treatment Centre (ETC): Pregnant and lactating women.[20] It highlights the importance of pregnancy testing where possible and counselling of pregnant women.

MSF advises that women who recover from their acute illness be offered a termination or induction of labour. This aims to reduce the high risk to others posed by a miscarriage or birth outside of the centre. Women who choose to continue their pregnancy are encouraged to stay close to the centre so they can be readmitted for the delivery.

The guideline reinforces that the safety of staff is the first priority. Surgical or invasive interventions should be avoided – this includes caesarean, uterine evacuation and episiotomy. Rupture of membranes should not be performed and vaginal examination should be kept to a minimum. In Sierra Leone there is a high rate of FGM, although less than ten per cent undergo infundibulation.[3] If possible deinfundibulation should be avoided. Oral medications should be used in preference to the intravenous or intramuscular route if possible. Prostin is used for induction of labour.

MSF recommends that live-born babies should be assumed to be infective and managed at the centre using full PPE. The mother should be allowed to breastfeed if she wishes to and is well enough. However, breastmilk is considered infectious although there have been no documented cases of transmission via breastmilk. When available, medication should be given to suppress lactation and for women with infants at home infant formula should be provided.[20] The guideline goes into much more detail, but otherwise the management of a pregnant woman is much like for any other Ebola case – supportive with routine antibiotic prophylaxis, antimalarial treatment, multivitamins, pain relief and fluids.[23] Women who are discharged should be offered effective contraception as well as condoms. Men are also discharged with condoms.

Although Hastings Airfield ETC has not been involved in any obstetric cases since the opening of MSF's unit, this protocol has provided useful guidance regarding early identification of pregnant women, contraception and lactation.

The situation has now improved dramatically in West Africa. As of the beginning of April, there were no cases in Liberia and less than a handful a day in Sierra Leone. Guinea, however, continued to have significant numbers of cases; with 57 being reported in the last week of March.[8] In Sierra Leone, schools have reopened as have most hospitals and healthcare centres. Sadly, however, the loss of healthcare workers will continue to be felt after the epidemic has been declared over.

Dr Cath Deacon worked with MSF in Lofa District in September and October 2014 before joining Aspen Medical to work at Hastings Airfield ETC as part of the Australian Ebola Response. She was the ETC's SMO from 1st December until mid-January.

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HPV vaccination program: the Australian experience

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Since 1991, Australia has had an organised approach to preventing cervical cancer. The National Cervical Screening Program (NCSP), using a Pap smear every two years in women aged 18–69, has resulted in a 50 per cent reduction in the incidence and mortality of this disease. In 2010, there were 818 new cases of cervical cancer in Australia and, in 2011, there were 229 deaths from this disease. The two-year participation rate for cervical screening in Australia is about 56 per cent and 80 per cent of Australian women will have had a Pap smear by five years. About 80 per cent of all new cases of cervical cancer arise in women who are under-screened or have never been screened. Cervical cancer is now the third commonest gynaecological cancer (behind endometrium and ovary) in Australian women and virtually all cases are caused by human papilloma virus (HPV) infection.

HPV causes cancer

In 1982, Harald zur Hausen demonstrated that HPV was the cause of cervical cancer. HPVs are DNA viruses that infect cutaneous or mucosal epithelium. There are more than 130 types of HPV of which 40 infect genital tract mucosa. They are classified into low- and high-risk types based on clinical outcome. Low-risk types cause benign anogenital warts and, of these, HPV 6 and 11 cause over 90 per cent of anogenital warts and recurrent respiratory papillomatosis. Infection with high-risk types cause virtually 100 per cent of cervical cancer, 90 per cent of anal cancers, 50 per cent of vulvar, vaginal and penile cancers, and 12 per cent of oropharyngeal cancers. HPV types 16 and 18 cause about 70 per cent of cervical cancers and HPV types 16, 18, 45, 31, 33, 52, 58 and 35 cause approximately 95 per cent of cervical cancers.

In most cases of HPV infection, the viral DNA is separated from the host genome as an episome (productive infection). However, when malignant transformation occurs the viral DNA is integrated into the host genome and there is expression of early proteins E6 and E7, which inactivate the tumour-suppressor genes p53 and retinoblastoma protein, respectively, allowing uncontrolled cell growth and carcinogenesis to occur. Preventing oncogenic HPV infection in women will prevent the development of cervical cancer, hence the recent introduction of a HPV vaccination program in Australia.

The vaccine

HPV cannot be grown in the laboratory, making the development of a live attenuated or killed vaccine impossible. Breakthrough research (Ian Frazer and his team) led to the development of 'virus like particles' (VLP) and subsequent development of a quadrivalent vaccine against HPV types 6,11, 16 and 18 (Gardasil) and a bivalent vaccine against types 16 and 18 (Cervarix). The HPV L1 capsid protein is the antigen in both vaccines and is produced by recombinant techniques. These proteins assemble themselves as VLPs identical to HPV virions, but with no DNA core.

Efficacy and immunogenicity studies showed Gardasil to be highly effective in preventing genital warts and both Gardasil and Cervarix almost 100 per cent effective in preventing HPV 16-18-related high-grade squamous abnormalities of the cervix (CIN2-3). Vaccination is highly immunogenic, generating high concentrations of neutralising antibodies to L1, and ongoing studies suggest protection for at least eight-to-ten years, with stable antibody titres strongly suggesting long-term protection.

The program

In 2007, a population-based National HPV Vaccination Program (NHVP) commenced in Australia. Gardasil was the only registered HPV vaccine in Australia at that time and was endorsed for use in the fully funded national program. This program aimed to deliver vaccine (three doses) to girls in school aged 12–13, a two-year catch up program for 13–18 year old girls through schools and a two-year catch up program for women aged 18–26 through GPs and community-based programs. The catch-up programs finished in 2009. A National HPV Vaccination Program Register (NHVPR) commenced in 2008. In 2013, a male program was commenced (12–13-year-old boys in school) with a catch up program for 14–15 year olds until the end of 2014.

School-based vaccination

There is strong evidence in Australia for school-based vaccination being the optimal method of delivery for adolescents. Initial coverage data showed that 70.7 per cent of girls who were 15 years of age in 2009 had received three doses of the vaccine and this level of coverage has been maintained. Catch up coverage data suggested good uptake for girls 14–17, but lower coverage rates for women aged 18–26 years. Under-notification to the HPV register of doses given to adult women in general practice means that the coverage estimates for older women are 5–15 per cent underestimated.

Vaccine safety

Adverse events following immunisation are notified to the Therapeutic Goods Administration that maintains a database. Local injection site reactions, nausea and fever are the most common symptoms notified as adverse reactions after vaccination. Syncope has also been documented following vaccination, but this is relatively common in the target age

group following vaccination and is not attributable to the HPV vaccine per se but to the injection process itself. Anaphylaxis has been rarely reported and all recipients should be observed for 15 minutes post injection. The international safety experience with HPV vaccines is now extensive, with over 210 million doses of HPV vaccines distributed globally, and the WHO Global Advisory Committee on Vaccine Safety having reviewed the vaccine regularly with no concerns raised. There is no association between vaccination and the occurrence of autoimmune, neurological or thromboembolic events.

Impact on disease incidence

This is a good news story with significant impact on disease prevalence within five years of starting the vaccination program. There has been a demonstrated dramatic fall in the prevalence of HPV vaccine types (6, 11, 16, 18) in women aged 18–24 years following the introduction of the program and some evidence of herd immunity. There is also some evidence of some cross protection for related HPV types 31 and 33.

There has been a significant fall in the detection rate of histologically confirmed high-grade cervical abnormalities and high-grade cytology in young vaccinated women compared with unvaccinated women. Eventually this will translate into reduced incidence and mortality from cervical cancer in vaccinated women.

There has also been a significant and marked decline in the incidence of genital warts in both females (vaccinated) and in males (herd immunity) as recorded by public sexual health services since the introduction of HPV vaccination in 2007. National hospital data has also shown a significant reduction in hospital admissions for genital wart-related treatments, in males and females, especially in the younger age groups and is the first evidence we have of an equal impact on disease burden among Indigenous Australians.

Participation

Coverage data available from the NHVPR shows an overall three dose completion rate of over 70 per cent of girls aged 12–13, with indications that this is rising further in the recent vaccination cohorts (75 per cent in 2012). Such coverage data are important and analysis provides information about who is being vaccinated and who is not, and this allows an investigation as to why not. Physician endorsement of vaccine usage is important as is a positive family vaccine attitude, but safety and cost are concerns for some along with a lack of knowledge about HPV and cervical cancer and how their daughter could possibly be at risk.

There have been concerns that vaccinated women would no longer see a need to participate in cervical screening. A recent Australian publication has shown a ten per cent fall in screening rates in vaccinated women aged 20–24, and 13 per cent in women aged 25–30. This is worrying and highlights the need for continuing education in this area.

The future

In 2014, the WHO approved the use of two-dose HPV vaccine schedules for those aged <15 years of age and some countries have commenced using these reduced dose schedules already (for example, the UK). The approval was based on demonstration of equivalent immunogenicity in this age group when two doses are given spaced at least six months apart (a prime-boost strategy) compared to the standard three-dose schedule (0, 1–2, six months) in older women that has known efficacy. This schedule has not yet been approved for use in Australia.

Australia is moving to a screening program with five-yearly primary HPV testing with partial genotyping (HPV 16-18) and cytology triage for other oncogenic HPV types. This is predicted to reduce the incidence and mortality from cervical cancer by about 22 per cent and the efficiency of this renewed program will depend on the continued high participation levels of women in the HPV vaccination program. All women, vaccinated or not, will need to continue to participate in the screening program as not all oncogenic HPV types are covered by the current vaccine.

A recently developed nine-valent HPV vaccine (Merck) has been shown to be effective and non-inferior to the quadrivalent vaccine (for HPV types 6, 11, 16, 18) and will provide additional protection against HPV types 31, 33, 45, 52 and 58, which are the next five most common HPV types detected in cervical cancers. This new vaccine has been approved by the FDA in the US and will be considered for use in Australia in the near future. If introduced, it has the capacity to prevent more than 90 per cent of cervical cancers and the associated pre-cursor lesions. If such a vaccine can be effectively delivered prior to sexual debut, women may only need to screen once or twice in a lifetime for almost complete protection against cervical cancer.

Conclusion

This is an exciting time for cervical cancer prevention in Australia. In 2017, we will have a new cervical screening program based on primary HPV testing and we already have a trail-blazing national HPV vaccination program.

The government-funded NHVP has been well received in Australia, with over a 70 per cent uptake in the target population. HPV vaccination has been shown to have a dramatic effect on oncogenic HPV prevalence, detection rates of high-grade CIN (histology and cytology), and the incidence of genital warts. The introduction of male vaccination, attempts to improve vaccination coverage in girls and boys, and the possible introduction of a nine-valent vaccine in the not-too-distant future should all lead to further improvements in cervical cancer prevention in Australia.

We must continue to strive for total participation in our screening program and maximal coverage in the HPV vaccination program. If both could be achieved we could conceivably eradicate cervical cancer in Australia. For now, cervical cancer is going, but sadly will not be gone for some time yet.

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HPV vaccination in low- and middle-income countries

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In a world of competing demands, healthcare decision-makers must assess vaccination programs, policies and practices by determining their potential healthcare gains relative to their economic costs. Decision-making in healthcare involves both a great deal of uncertainty and substantial consequences. Cost-effectiveness analysis (CEA) is used to evaluate a specific intervention relative to the current practice. Through determining effectiveness, safety and cost, cost-effectiveness research can guide the allocation of scarce resources to achieve the greatest public health gains. By carefully synthesising economic, surveillance and epidemiologic data, CEA provides a scientific framework central to evidence-based public-health practice.

A few ethical challenges arise when considering the field of CEA. First, CEA is a public health science that seeks to maximise health gains relative to economic costs. Social concerns such as prioritising the sick, young and reducing healthcare inequities are not explicitly built into these mathematical models. Therefore, decision-makers must take CEA work together with social and economic factors outside of the model into consideration. Second, CEA is not designed to address limitations of the current practice, nor is it designed to identify misallocation of resources. Therefore, factors outside of the cost-effectiveness model, such as sustainability, must also be considered. Third, CEA is largely economically prohibitive for many low- and middle-income countries (LMIC). This is of particular concern as LMIC typically have the most to gain from cost-effective interventions.[1]

As a rule, vaccines provide the greatest bang for the public health investment buck. The costs associated with vaccination delivery are a fraction of those attributable to treatment, income loss, disability and death owing to illness and generally provide lifetime protection. Vaccines provide direct medical savings and indirect economic benefits through improved health and increased life expectancy. Even with newer and more expensive vaccines, vaccination remains one of the most cost-effective public health measures.[2]

However, the World Health Organization (WHO) recommends that every country carefully consider specific costs, logistics, staffing, sustainability and impact of national vaccine programs prior to adoption.[2] High-income countries (HIC) historically complete assessment and initiate vaccination rollout prior to LMIC while the impact of these programs are equally, if not more, beneficial for countries with limited public health funds. Additionally, assessments of cost-effectiveness require complex models using data that are often unavailable in many resource-poor settings. Essentially, countries best served by timely vaccination programs are hindered by between-country disparities. Given these challenges, decision-makers in LMIC must carefully consider analytic options.[3]

Specifically, HPV is responsible for 27 500 premature deaths annually from cervical cancer occurring in adulthood, 85 per cent of which occur in the poorest, low-income countries.[4] In many countries cervical cancer is responsible for more deaths than childbirth. HPV vaccination must be administered before sexual debut as it is only effective before the person is infected.

Recently, the WHO convened an expert panel to help guide economic analysts in supporting decisions about HPV vaccination programs in LMIC. The panel developed a series of questions to help decision-makers determine appropriate economic analyses. The first question decision-makers must address is whether to develop a new model, adapt an existing one or not conduct an economic evaluation at all. While developing a new model with country-level data is optimal from an information perspective, the choice to forgo economic evaluation is attractive for resource-limited LMIC. Decision-makers should also give serious consideration to adapting an existing model rather than creating a new one. When key model parameters are stable or easily modified, conducting a new analysis may add little value. For example, research has found the key drivers of cost effectiveness of HPV vaccines in LMIC are: vaccine price, HPV prevalence and uptake of cancer screening and treatment.[5-6] Therefore, studies examining similar policy questions in similar settings may be best suited to adapt an existing model.

After addressing the question of whether an economic analysis is needed, the next question is whether analyses should address costs, epidemiological outcomes or both? This choice should be based on a clear policy question. Typically, an analysis will include both epidemiological and economic outcomes and will be presented with multiple audiences in mind. Assuming costs are considered, costing methodology and analytics must be carefully planned. The types of outcomes to be presented must be driven by policy and can range from static models with simple demographic and epidemiological data requirements to dynamic progression models that require complex clinical data.[3]

Every model includes uncertainty in methodology, structure and input parameters. This uncertainty must be clearly addressed in order to demonstrate the impact of varying particular assumptions. Based on the target

audience, decision-makers must determine how best to communicate results of cost-effectiveness models. Simpler models have more uncertainty as a function of limited inputs but are easier to disseminate.[3]

One example of an existing model that makes good use of available data and that can be used in LMIC, is the Papillomavirus Rapid Interface for Modeling and Economics (PRIME) model developed to assess cost-effectiveness and health effects of vaccination of girls against HPV before sexual debut in terms of burden of cervical cancer and mortality. The WHO Commission on Macroeconomics and Health classified healthcare interventions that cost one to three times the GDP per capita per disability-adjusted life year (DALY) averted as cost-effective and those that cost less than one GDP per capita per DALY averted as very cost-effective.[2] The PRIME model found that in all LMIC, except Afghanistan and the Democratic Republic of Congo, HPV vaccination is very cost effective. This global analysis is in agreement with previous research suggesting that HPV vaccination is cost effective in nearly all countries, particularly low-income and low-middle-income countries. [7]

In summary, HPV vaccination is a solid public health investment. HPV is highly prevalent throughout the world and the greatest gains in decreasing related cancers and death can be achieved in the poorest countries, particularly those without existing HPV vaccination programs. Decision-makers are encouraged to use tools available, such as the PRIME model, to inform HPV vaccination policy – especially in resource-poor settings. In addition, long-term and societal economic benefits of decreased HPV prevalence, outside the scope of cost effectiveness analysis, should be considered.

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HPV testing explored and explained

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Harald Zur Hausen was awarded the Nobel Prize for Medicine, in 2008, for the isolation and characterisation (in 1983) of human papillomavirus (HPV) 16 as a causative agent in cervical cancer. The first evaluation of HPV testing in a potential clinical application was published by John Tidy et al, in 1989, on the detection of HPV by polymerase chain reaction (PCR) in normal and dyskaryotic cervical smears from 21 women. They ventured that HPV testing might eventually supplement cytological analysis in cervical screening.

HPV types

There are approximately 40 different types of HPV that infect the cervix. Some of these viruses have the ability to integrate the HPV genome into the epithelial cell genome and thus become carcinogenic. The International Agency for Research on Cancer (IARC) has classified 12 HPV types as Group 1 carcinogens – HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59. These are known as oncogenic or high-risk (hr) HPV types. HPV 68 is classed by IARC as a Group 2A carcinogen (probably carcinogenic to humans) and there are several HPV types classed by IARC as group 2B (possibly/rarely carcinogenic to humans). HPV 16 is by far the most carcinogenic in terms of numbers of cases of cervical cancers and causes the most cancers linked to HPV in other anogenital epithelia and in the oropharynx.

Screening program and Renewal

HPV testing was first introduced to the Medicare schedule in Australia with the adoption of the 2005 NHMRC guidelines for the management of asymptomatic women with screen-detected abnormalities. It was recommended for the follow up of high-grade squamous intraepithelial lesions (HSIL) at 12- and 24-months post treatment. At that time the method of HPV detection was not prescribed.

In May 2017, Australia will change the National Cervical Screening Program from primary screening by cytology to primary screening with HPV testing. This is despite Australia having an extremely successful screening program based on cytology. The reasons for the change are that, while the program is effective in ensuring low incidence and mortality rates of cervical cancer (among the lowest in the world), it is relatively intensive compared with other countries. There have also been significant advances in our understanding of the development of cervical cancer. It is now known that infection with HPV is a necessary prerequisite for its development. There is new evidence for alternative pathways for cancer screening and prevention. Ian Hammond's article (see p28) documents the effects of the HPV vaccination on the Australian population, giving further impetus to examining different screening tests, target age range and screening intervals.

Trials on HPV testing

HPV testing has been studied in a number of different contexts:

1. information on rates of persistence of HPV infection;
2. investigation of regional and international prevalence of HPV types;
3. identification of HPV type distribution in cancers;
4. triage of women with equivocal or low-grade cytology;
5. follow up of women after treatment for cervical intraepithelial neoplasia; and
6. primary screening for cervical cancer precursors, either alone or in combination with cytology.

As a result of points one to three, we know the following

- The majority of HPV infections are transient, most clearing within a few years. However, some persist and it is these persistent infections that may lead to development of precancerous changes.

The prevalence of different HPV types is different in different regions of the world, but worldwide HPV 16 and 18 are the most common high-risk types and approximately 70 per cent of cervical cancers are caused by one of these two genotypes.

HPV as primary screening

Trials examining HPV testing as a primary screening tool have included studies in high-resource settings, such as Australia, and also a study in India, comparing a single HPV test with a single cytology test in a previously never-screened population in a low-resource setting. The latter showed that a single HPV test could significantly reduce the incidence and mortality of cervical cancer compared with the single cytology test. The trials in high resource settings have shown that at five years the incidence of HSIL is lower after a negative HPV test than a negative Pap smear. Also, negative predictive value of a negative HPV test lasts twice as long as a negative Pap smear; thus allowing for longer screening intervals.

In late 2012, the Netherlands became the first country in the world to announce it would change its screening program from cytology to primary HPV screening. The program is expected to commence in January 2016. In November 2011, the Department of Health and Ageing commenced a review of the Australian program, called the Renewal of the National Cervical Screening Program.

Renewal

The Medical Services Advisory Committee commissioned a review of the evidence for specified screening pathways and an economic modelling and health outcomes review. After a robust process, they made the following recommendations:

- five-yearly HPV test with partial genotyping;
- reflex liquid based cytology triage;
- age range of screening 25–69 years;
- exit HPV testing age 70–74 years;
- the program remain the same for HPV vaccinated and unvaccinated women; and
- self-collection HPV test be available for underscreened and never-screened women.

On 19 September 2014, the Australian Health Ministers' Advisory Council endorsed the recommendations and a draft interim implementation plan.

Technical aspects of HPV testing

Unlike conventional cytology, HPV testing is not one test, but rather a number of different technologies. Many of the original trials on its validity were done using hybrid capture technology. The hybrid capture technology (HC2, Qiagen) is based on a RNA probe binding to the DNA target to form a RNA:DNA hybrid. Amplification (x3000) and detection of RNA:DNA hybrids by means of multiple labelled antibodies shows the presence of 13 high-risk antibodies (not individually identified).

A refinement of the Hybrid Capture 2 technology makes use of hybridisation followed by signal amplification using invader technology. This third-wave invader HPV test (Cervista, Hologic) allows for partial HPV 16 and 18 genotyping.

The other main method of HPV testing is polymerase chain reaction (PCR), which involves amplification of the target sequences in the L1 (a HPV protein) open reading frame (ORF) of the HPV nucleocapsid. It is flexible, has the greatest sensitivity, can be used for detection, quantitation, sequencing, mutation analysis and there are multiple available formats. As well as in-house laboratory PCRs, there are commercially available PCR technologies, including Abbott real-time HPV test and Roche Cobas 4800. Partial HPV genotyping is available with these tests.

Another means of testing for hrHPV infection is detection of mRNA of E6/E7. This method is used by GenProbe for its APTIMA test, which has shown greater specificity than other HPV tests.

Validated HPV tests

In 2009, Meijer et al published the guidelines for HPV DNA test requirements for primary cervical cancer screening in women aged 30 years and older (this was accepted internationally as the 'Meijer criteria' for HPV testing). They require that to be validated the test must demonstrate non-inferiority to the HC2 test in terms of sensitivity and specificity and there should be intra-laboratory reproducibility.

HPV Test for Australian NCSP

Since the strength of the HPV test is its negative predictive value and women will only be tested every five years; it is essential that any HPV test used for screening be a validated test that has demonstrated robust performance in a screening environment. In addition, the program has decided to perform partial genotyping to identify HPV types 16, 18 and, possibly, 45. The reason for this decision is that these types are considerably more oncogenic than the other high-risk HPV types, accounting for more than 70 per cent of all cervical cancers. Thus, the tests accepted as part of the screening program will need to be capable of partial genotyping.

Biomarkers

It is known that the majority of infections detected by HPV testing will be transient and will not result in precancerous or cancerous lesions. In the future, in addition to using partial genotyping to improve specificity, biomarkers may be used to differentiate these transient infections from the potentially more serious integrated infections. There have been many markers identified and examined; one such, which has been used in some trials to improve specificity, is p16INK4a. The published literature indicates improved specificity, but at the cost of sensitivity. Other potential biomarkers, such as the loss of L1 capsid expression, have also been explored.

Future

In Australia, we are moving to an exciting situation where we could anticipate the near eradication of cervical cancer. The combination of HPV vaccination as a primary prevention strategy and improved secondary prevention with more sensitive screening tests, longer screening intervals and improved detection rates, augurs well for the future health of Australian women.

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Viral hepatitis in pregnancy

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Viral hepatitis is reported to be the most common form of liver disease in pregnancy. Australia and New Zealand are low-prevalence areas for viral hepatitis; but, particularly with inward migration from high-prevalence regions, a significant number of women with viral hepatitis in pregnancy are likely to be encountered in clinical practice. This article will focus on the most common viral hepatitides in Australia and New Zealand – hepatitis B and C – but hepatitis A, D and E will also be briefly discussed.

Hepatitis B

Incidence in pregnancy

The prevalence of hepatitis B (HBV) in Australia and New Zealand is low, with 0.1 per cent to two per cent of the general population infected. The prevalence in pregnancy largely mirrors that in the general population, but in pregnant immigrants this reflects the prevalence in their birth country. A recent Australian study reported an overall prevalence of HBV in pregnant women of 0.75 per cent, but rates of 6.5 per cent to 8.6 per cent in women from Asia and the Pacific.[1]

Impact of pregnancy on HBV

Acute HBV in pregnancy is uncommon and its course appears unaltered by pregnancy though the likelihood of progression to chronic carriage may be increased by pregnancy. In chronic HBV, women with cirrhosis are at increased risk of decompensation and variceal bleeding during pregnancy and advanced disease should be excluded in patients not previously assessed. However, most pregnant patients with chronic HBV will not have severe disease and, although hepatic flares or even acute liver failure may rarely occur, in the majority the liver disease will be unaffected by pregnancy. Postpartum flares are common, but usually mild and asymptomatic. In a recent Australian study postpartum flares occurred in 25 per cent of pregnancies, but alanine transaminase (ALT) was less than 5xULN in two-thirds of patients and all remained asymptomatic throughout.[2]

Impact on pregnancy of HBV

Studies of pregnancy outcomes in women with chronic HBV have produced inconsistent results with no adverse effect in some, but increased risk of obstetric complications and neonatal morbidity in others. A large Israeli study found increased rates of low birthweight, perinatal mortality, congenital malformations, premature rupture of membranes and placental abruption in women with chronic HBV.[3] An increased incidence of threatened preterm labour, preterm birth and antepartum haemorrhage has also been demonstrated. Gestational diabetes also appears more common in women with chronic HBV.

Mother-to-child transmission

Mother-to-child transmission can occur in up to 90 per cent of cases without immunoprophylaxis. Risk of transmission correlates with maternal viral load, with transmission to 70–90 per cent of infants born to high viral load eAg+ve mothers, but only 10–40 per cent in infants born to low viral load eAg-ve mothers. Most transmission occurs at birth. As a consequence, immunoprophylaxis with HBV hyperimmune gamma globulin (HBIG) within 12 hours of birth and subsequent HBV vaccination provides up to 95 per cent protection against perinatal infection. However, immunoprophylaxis failure may occur in women with very high viral loads. A number of studies have demonstrated that immunoprophylaxis failure is frequent with a viral load >8 log copies/ml (7 log iu/ml), but unlikely below this level.[4]

With regards to obstetric management, there is no definite evidence caesarean section, rather than vaginal delivery, reduces transmission. Although HBsAg is detectable in breastmilk, perinatal infection rates are the same in breastfed infants as formula-fed infants and breastfeeding is not contraindicated in infants who have received immunoprophylaxis.

Treatment of HBV in pregnancy

Data from the Antiretroviral Pregnancy Register have suggested that the oral antivirals tenofovir and lamivudine are safe in pregnancy, without any increased risk of birth defects. Telbivudine also appears safe, though fewer studies are available. Adefovir and entecavir are avoided in pregnancy as safety data are lacking. Tenofovir is the drug of choice in pregnancy and in breastfeeding mothers as viral resistance is unreported and the drug does not appear at significant levels in breastmilk.

The use of antiviral drugs during pregnancy is indicated for control of maternal liver disease or to prevent mother-to-child transmission. In patients already on antivirals before conception or in early pregnancy, the options are to stop treatment or continue with a drug safe in pregnancy. Patients with advanced fibrosis or cirrhosis should continue antiviral treatment to avoid disease progression or decompensation. In patients without severe disease, continuing treatment is advised to prevent flares.

In patients with active disease (elevated ALT and HBV DNA >105 iu/ml) not on treatment, the use of antiretrovirals should be considered. In patients with inactive disease (normal ALT), but high viral loads, current national guidelines do not recommend treatment.[5,6] However, there is now strong evidence that antivirals commenced in late pregnancy prevent transmission. Two recent studies, one using telbivudine and the other tenofovir, showed dramatic reduction of transmission rates in women with high pre-treatment viral loads.[7,8] The use of tenofovir, or telbivudine from 28 weeks gestation should therefore be strongly considered in women with viral loads >7 log iu/ml. Continuation of treatment for up to 12 weeks after delivery to reduce postpartum flares and promote eAg seroconversion has been suggested. However, a recent Australian study showed no difference in the incidence of postpartum flares or eAg seroconversion rates whether antiviral treatment was stopped early, late or not used at all.[9]

Hepatitis C

Incidence in pregnancy

Approximately 2.7 per cent of the Australian and New Zealand population are positive

for hepatitis C (HCV) antibodies, indicating prior exposure. Studies in Australian obstetric populations have shown anti-HCV positive rates from 1.1 per cent to 1.4 per cent. Of these women, 45–70 per cent will be chronically infected with virus.

Impact of pregnancy on HCV

There have been only rare reports of acute HCV during pregnancy, but these few case reports are not suggestive of a poorer outcome in pregnant individuals.

In chronic HCV infection, cirrhosis is associated with increased risk of decompensation and portal hypertensive bleeding during pregnancy. However, the majority of pregnant women with chronic HCV will not have advanced liver disease and therefore pregnancy will not adversely affect their liver disease. Indeed, elevated ALT in early pregnancy often normalises in late pregnancy, suggesting a decline in immune-mediated inflammatory activity during pregnancy. Transaminases typically rebound postpartum and there have been reports of worsening liver histology associated with this. However, overall, pregnancy appears to have little impact on the course of HCV-related liver disease.

Intrahepatic cholestasis of pregnancy (ICP) does appear to be associated with HCV infection. Women diagnosed with HCV have a >5-fold increase risk of ICP and it appears to occur earlier in pregnancy in women with chronic HCV.[10]

Impact of hepatitis C on pregnancy

The results of studies investigating the impact of chronic HCV on pregnancy outcomes have been conflicting. Some have not demonstrated any detrimental effect while others have shown a modest increased risk of adverse maternal and neonatal outcomes. Increased rates of preterm birth, low birthweight, need for neonatal assisted ventilation and need for neonatal ICU admission have been reported.[11] Higher rates of gestational diabetes, gestational hypertension and antepartum haemorrhage have also been described.

Mother-to-child transmission

The rate of transmission of HCV from mother to child is low. In a recent meta-analysis the pooled risk of vertical transmission from HCV-ab positive/HCV RNA positive/HIV negative mothers was 5.8 per cent, but 10.8 per cent from HCV/HIV co-infected mothers.[12] HCV viral load determines risk of transmission. Transmission does not occur from HCV-ab positive/HCV RNA negative women while in HCV RNA positive women, viral load correlates with transmission risk. A recent study showed transmission rates of 14.8 per cent at viral loads ≥6 log copies/ml, but only 3.9 per cent at viral loads below this level.

Premature rupture of membranes more than six hours before delivery and use of

internal fetal monitoring have been shown to increase transmission risk.[13] Vaginal delivery is not associated with higher risk of transmission then caesarean section.[14] HCV does not appear to be transmitted from breastfeeding mothers to infants, despite HCV RNA being detectable in colostrum, and breastfeeding is therefore not contraindicated except in mothers with cracked or bleeding nipples.

Treatment during pregnancy

Pegylated interferon and ribavirin-based treatments for HCV are contraindicated in pregnancy. New oral antiviral agents, which are highly efficacious with few side effects, have been developed and are likely to be available soon. However, their safety in pregnancy has not yet been established. Furthermore, given the low rates of vertical transmission, treatment during pregnancy may not be warranted.

Hepatitis A

The incidence of acute hepatitis A (HAV) in the general population in Australia and New Zealand is low, but even in higher prevalence regions acute HAV in pregnancy is uncommon.

Pregnancy does not appear to adversely affect the course of acute HAV. However, pregnancy complications appear common, with reports of premature contractions and premature rupture of membranes in up to 69 per cent of pregnancies in acute HAV patients. Mother-to-child transmission of HAV may occur, and neonatal icteric hepatitis has been reported, but is uncommon owing to protective maternal anti-HAV IgG antibodies crossing the placenta.

There is no specific treatment for HAV and hence management is supportive. HAV vaccine is safe in pregnancy and should be considered in non-immune pregnant women travelling to endemic areas.

Hepatitis E

Hepatitis E (HEV) is the most common cause of viral hepatitis in pregnancy globally, particularly in hyper-endemic areas such as India. However, HEV is a rare cause of symptomatic hepatitis in Australia and New Zealand, but should be considered in pregnant women with acute hepatitis who have travelled to a high-prevalence area.

The course of acute HEV is worse in pregnant than non-pregnant women, and also worse than that of other viral hepatitides in pregnancy with fulminant hepatic failure (FHF) reported to be almost seven times more common in pregnant women than non-pregnant women HEV. Progression to fulminant hepatic failure has also been reported to be almost three times more common in pregnant women with HEV than in non-HEV acute hepatitis. Mortality is up to 20 per cent in pregnant women with acute HEV.

Acute HEV also worsens pregnancy outcomes: antepartum haemorrhage, intrauterine death and preterm delivery all occur at increased frequency. Vertical transmission of HEV has been reported to occur in up to 79 per cent of cases, with icteric or anicteric hepatitis developing in most infected infants, leading to death in almost 50 per cent.

There is no specific treatment for acute HEV, and management is therefore supportive. A safe, effective vaccine against HEV genotypes 1 and 4 has been developed (Hecolin®). Data from a small number of women suggest it is safe in pregnancy.

Hepatitis D

Hepatitis D (HDV) is a defective RNA virus that only exists as a co-infection with HBV. Approximately four per cent of HBV carriers worldwide have been exposed to hepatitis D. It is significant because both acute infection and chronic infection follow a more severe course than HBV mono-infection. In particular, chronic disease progresses more rapidly to cirrhosis.

Perinatal transmission is uncommon and nucleos(t)ide analogues are ineffective against HDV, but identifying pregnant patients with chronic HDV infection is important because of the increased likelihood of underlying advanced liver disease.

Conclusions

In the majority of women with viral hepatitis, pregnancy does not have a significant impact on their liver disease. However, it is still important to identify these patients given pregnancy outcomes may be negatively affected and also, in some cases, intervention may reduce the risk of the transmission of viral hepatitis to the infant.

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Viral gastroenteritis and hepatitis A in pregnancy

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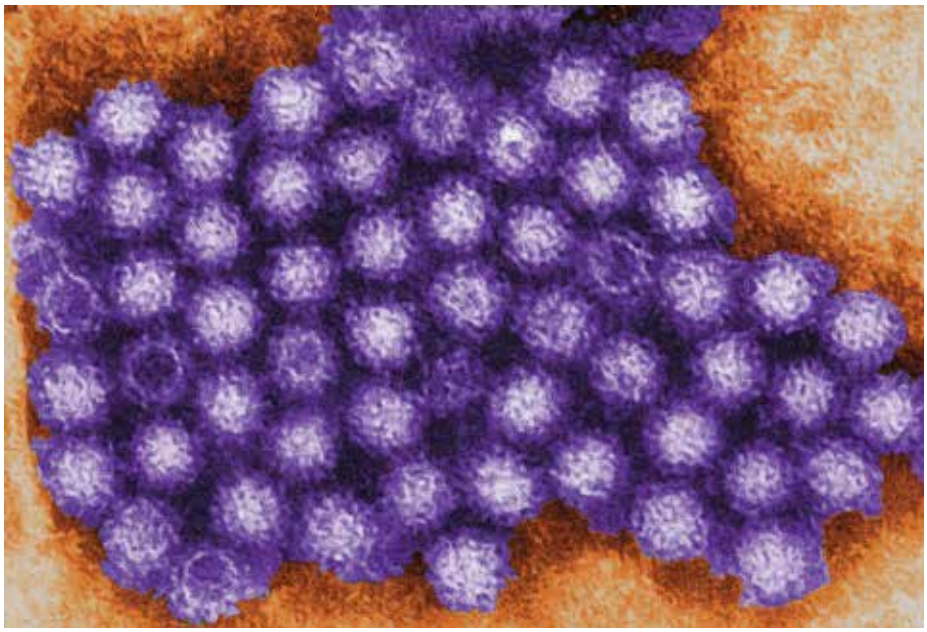
Gastroenteritis is a general term for any inflammation or infection of the gastrointestinal tract, but in common clinical usage it refers to episodes of nausea, vomiting and diarrhoea. In the general community, the usual causes of acute gastroenteritis are viral infections and bacterial food poisoning. The pathogen typically associated with outbreaks of infectious gastroenteritis in adults is norovirus. Episodic causes in adults include norovirus, but also commonly rotavirus and adenovirus. Infants often suffer from rotavirus in outbreak settings.

Noroviruses are non-enveloped single-stranded RNA viruses that belong to the Caliciviridae family. They are very infectious, with a single person often infecting as many as 12 other people. Noroviruses are classified into six genogroups of which G1, GII and GIV infect humans, most commonly GII. It is thought that the MDA-5 protein in humans is the primary immune sentry for detection of norovirus and individuals with common mutations of the MDA-5 gene seem to be more susceptible to infection by norovirus. When infection occurs the virus infects and replicates in the small intestine, leading to inflammation and onset of symptoms within a day or two. Although the infection is self-limiting, vulnerable people – the elderly or immunocompromised and children – are most vulnerable to dehydration and electrolyte disturbances, and deaths still occur from acute norovirus gastroenteritis.

In the initial stages of illness, it can be difficult to determine whether gastroenteritis is viral or from bacterial food poisoning. However, some features may help distinguish between the two. Food poisoning is typically associated with diarrhoea, abdominal cramping and vomiting, and fever may be present. Viral gastroenteritis is less likely to cause significant fever or bloody diarrhoea.

Norovirus gastroenteritis has a typically sudden onset of nausea and vomiting. The vomiting can be profuse and violent, occurring without warning and many times during a day. There is associated malaise, headache, myalgias and sometimes fever, and watery diarrhoea can also occur. Fortunately, these symptoms are relatively short lived, lasting only one or two days. Although diagnosis can be made using polymerase chain reaction (PCR) testing of faecal samples, this is more useful at a community public-health level than for individual cases and is not performed for routine diagnosis.

Norovirus infection is highly contagious, with direct transmission from person to person, airborne spread by aerosolised vomit, ingestion of food or drink contaminated with norovirus, and contact with contaminated surfaces or objects. It is generally stated that people are infectious from the day that symptoms commence. Viral shedding, however, can occur before symptoms begin and can persist for two or more weeks after the acute illness ends. It is not known whether viral shedding is indicative of infectivity. To reduce the risk of infection to others, it is usual to be excluded from work until there has been no diarrhoea for 24 hours.



Transmission electron micrograph (TEM) image of some of the ultrastructural morphology displayed by norovirus virions, or virus particles. Image credit: Charles D. Humphrey, courtesy of the Centers for Disease Control and Prevention.

Differential diagnosis

Common things occur commonly and the typical picture of acute onset of symptoms in a previously well woman, often during a period of community outbreak and with other family members or contacts affected with the same illness, points strongly to viral gastroenteritis. However, in pregnancy it is important to consider other causes (see Box 1). Food poisoning typically occurs within a few hours of ingestion and may simultaneously affect others sharing the same food. Surgical causes often have vomiting without the associate nausea. Emerging infections such as *Clostridium difficile* colitis may be difficult to exclude clinically if there is concomitant hyperemesis and can occur without clear antibiotic exposure. Pregnancy-specific conditions – hyperemesis, acute fatty liver and severe pre-eclampsia – will have their own symptom complex.

Assessment

Dehydration is assessed by clinical examination, looking for reduced skin turgor and dry mouth and tongue. There is commonly tachycardia and postural hypotension, though these can be more difficult to interpret in pregnancy. The fetal heart should be auscultated. There is little role for investigations if the clinical history is clear, but electrolytes and renal function and full blood count might be assessed. To distinguish from pregnancy-specific causes, checks of uric acid and liver function might be made. Acute fatty liver is characterised by low blood glucose levels, high white cell count and abnormal liver function.

Treatment

There is no specific treatment for norovirus infection in pregnancy and, unfortunately, no vaccine available. Oral rehydration and parenteral or oral antiemetics (metaclopramide or ondansetron) are the mainstays of treatment. It is important to manage pregnant women as outpatients if possible, as norovirus infection can sweep quickly through a maternity ward and affect neonates. For women who are not tolerating oral rehydration, intravenous fluids may be required. Strict infection-control procedures should be in place, including meticulous attention to the five moments of hand hygiene.

Hepatitis A

Recent cases of hepatitis associated with imported frozen berries have drawn attention to hepatitis A. Hepatitis A virus (HAV) is a small RNA virus, or picornavirus. It is not enveloped and, like norovirus, contains a single strand of RNA enclosed in a protein shell. Although HAV has only one serotype, there are many different genotypes; four of which affect humans, the commonest of which is the IA subtype.

HAV spreads by the faecal-oral route and is common where there is overcrowding with poor hygiene and sanitation. HAV is very hardy and is resistant to the action of detergents, desiccation and high temperatures. For this reason, HAV can survive for long periods in water. Fortunately, chlorination of drinking water is an effective way of inactivating the virus. Infection is common in the developing world (where it approaches 100 per cent) and usually occurs in early childhood. In Australia, childhood infection is uncommon except in the Aboriginal and Torres Strait Islander population in Queensland, Northern Territory, South and Western Australia. For this reason, it is included in the National Immunisation Program Schedule for those aged 12–24 months from these high-risk populations. Parenteral transmission, for example by blood products, is now very rare. Outbreaks associated with food such as shellfish are common, particularly if the shellfish have been sourced from polluted waters.

Once ingested, the HAV particles cross into the circulation through the digestive mucosa and are carried to the liver by the portal circulation. HAV infects hepatocytes and liver macrophages, and then multiplies with cell breakdown and release of new HAV particles through the bile into the faeces. Unfortunately, infected individuals often excrete large numbers of infectious HAV in the stool for more than a week before the onset of symptoms. Therefore, people infected with HAV can be infectious before there is a recognisable onset of symptoms and for almost a fortnight after the acute infection has passed. The incubation period is long, averaging a month, meaning that the source of infection may be long forgotten, making source tracing difficult.

Clinical presentation

The initial symptoms of acute hepatitis A are non-specific with an influenza-like illness or, in some cases, few symptoms at all. The illness can last for up to two months, but sometime considerably longer. Typical presentation is with jaundice, dark urine, anorexia, low-grade fever, fatigue, nausea and diarrhoea with light (clay coloured) stools. You are more likely to experience symptoms the older you are at the time of infection.

Diagnosis is based on clinical suspicion and isolation of IgM against HAV. If the test is negative at initial presentation, a four-fold rise in HAV IgM is also diagnostic (presence of IgG suggests that the infection is not acute). There may be an increase in serum ALT levels. There is no treatment for hepatitis A, apart from avoidance of alcohol (which is often poorly tolerated), healthy diet (avoidance of fatty foods) and good hydration. There is no particular risk to the fetus in pregnancy, but it is important to distinguish acute hepatitis A from other causes, including pre-eclampsia, HELLP syndrome and acute fatty liver. For women with a significant travel history and jaundice, hepatitis E is important to exclude as fetal risk includes spontaneous abortion and premature delivery. Maternal liver failure can also occur. The mortality rate from hepatitis A in otherwise healthy people is very low.

An effective vaccination against HAV is available and recommended for those at risk. The vaccination contains a live, attenuated virus, so should not be given in pregnancy.

Box 1. Differential diagnosis of acute nausea and vomiting in pregnancy

General
- Acute viral gastroenteritis
- Acute bacterial food poisoning
- Clostridium difficile colitis

Pregnancy specific
- Severe nausea and vomiting of pregnancy (hyperemesis gravidarum)
- Acute fatty liver of pregnancy
- Severe pre-eclampsia

Non-infectious
- Ovarian torsion
- Surgical causes – acute cholecystitis, appendicitis, small bowel obstruction, pancreatitis
- Hepatitis
- Diabetic ketoacidosis

Influenza virus in pregnancy

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Data from the influenza pandemic of 2009 confirmed known observations from previous seasonal epidemics and pandemics: pregnant women are at increased risk for severe influenza virus infection. Higher rates of hospitalisation, fetal loss and maternal death are well-recognised complications of influenza virus infection in pregnancy, particularly during the late gestational period. The safe and immunogenic influenza vaccine is the only proven method to prevent influenza infection and should be prioritised in pregnant women.

Influenza viruses are single stranded, negative sense RNA viruses belonging to the family *Orthomyxoviridae*. Within this family, influenza virus types A and B primarily cause human infection. Influenza virus infection occurs when the surface glycoprotein haemagglutinin (H) binds the sialic acid-containing receptors on target host cells to initiate infection. Following viral replication, neuraminidase (N) cleaves sialic acids from cellular receptors and extracellular inhibitors to facilitate progeny release and spread to neighbouring cells (see Figure 1).

Influenza A viruses are also subtyped based on the haemagglutinin and neuraminidase glycoproteins, for example, influenza A/H1N1, H3N2 and avian influenza A/H5N1 and H7N9. A remarkable feature of influenza viruses lies in their ability to undergo antigenic variation. Antigenic drifts result from point mutations in the haemagglutinin and neuraminidase genes, which allow the virus to evade the human immune response, resulting in seasonal epidemics. This potentially necessitates annual changes in the influenza vaccine. Antigenic shifts occur when a new influenza subtype emerges, or from the reassortment of haemagglutinin and neuraminidase genes between human and non-human (avian or swine) subtypes. Owing to the lack of pre-existing cross-protective antibodies in susceptible populations, global epidemics or pandemics result.

The burden of influenza infection is typically underestimated as symptoms of influenza are not specific to influenza virus per se and infection may not be laboratory confirmed. In Australia, modelling suggests that 310 000 general practice consultations and 18 400 hospitalisations result from influenza infection annually, at an estimated cost of $115 million.[1] In New South Wales, influenza and pneumonia were responsible for 9.1 per cent of total deaths in 2013 (available at: www.health.nsw.gov.au/Infectious/Influenza/Documents/2013/december-report.pdf).

Severe influenza infection in pregnant women was first noted during the influenza pandemic of 1918, with reported mortality rates of 27–45 per cent. This has also been consistently observed in subsequent pandemics, in which infection in pregnant women was associated with an increased risk of both severe complications and death.[2-5] During the influenza A pandemic of 2009, 9.1 per cent of patients admitted to intensive care units (ICUs) in Australasia were pregnant (approximately ten times the incidence of pregnancy in the community) and mortality rates were approximately 8.6 per cent.[6] In Victoria, 51 per cent of pregnant women with complicated influenza had an additional comorbidity, including asthma, smoking and/or diabetes, but the remainder had no additional risk factor for severe influenza infection.[7]

Poor outcomes from influenza infection in pregnancy are not attributable to anatomical and physiological changes in the respiratory tract alone (such as reduced functional residual capacity, increased oxygen consumption or progesterone induced hyperventilation). Pregnancy is associated with a generalised state of immune tolerance or immunosuppression, with increased severity and susceptibility to infections including, but not limited to, listeriosis, malaria and hepatitis E virus. Pregnancy is also associated with a bias towards Th2-associated humoral immunity as a predominant Th1 cell-mediated immune response is harmful to the fetus, characterised by low peripheral natural killer cell activity.[8] Of note, there is increased expression of pro-inflammatory cytokines such as IL-6, IL-8 and TNF-α following maternal influenza virus infection.[9]

The direct effects of maternal influenza infection on the fetus are not well studied or understood at present. Maternal viraemia and transplacental transmission following influenza infection are uncommon, yet adverse fetal outcomes in the absence of direct fetal infection have been observed.[10] Increased rates of spontaneous miscarriage, low birthweight, preterm delivery and fetal

death have been observed and reported, mainly during influenza pandemics.[11-14] A recent review of non-chromosomal congenital abnormalities noted the increased risk of hydrocephaly, cleft lip, neural tube defects and congenital heart defects following maternal influenza infection or influenza-like illness during the first trimester.[15] Another potential added risk of influenza infection is maternal hyperthermia, known to have an association with neural tube defects.[16,17] However, this risk is mitigated by the relatively short duration of fever and response to antipyretics in influenza infection.

Influenza virus is easily spread from person to person via coughing and sneezing, resulting in small-particle aerosols that can remain suspended in the air for many hours, or by direct contact with an infected individual or environments contaminated with respiratory secretions. Clinical manifestations of influenza infection in pregnant women are similar to those of the general population. After an incubation period of one to three days, typical symptoms include fever, sore throat, rhinorrhoea, cough, shortness of breath and myalgia. Infection can range from mild and self-limiting to severe and life-threatening when complicated by primary viral pneumonitis or secondary bacterial pneumonia and other less common complications such as kidney injury and encephalopathy.

Laboratory confirmation of influenza guides treatment, obviates the need for further unnecessary testing and informs infection control procedures and vaccination strategies.[18] When selecting the most appropriate test, clinicians should consider the availability, performance and turnaround times of the different diagnostic methods, such as antigen detection, viral culture and nucleic acid tests (NATs). Influenza diagnostic tests can be performed on upper and lower respiratory tract samples, including nose and throat swabs, nasopharyngeal swabs, bronchoalveolar lavage fluid and pleural fluid. Sputum is not a preferred specimen owing to its viscosity.

The sensitivity of influenza diagnostic tests may be increased when lower respiratory tract samples are tested. The detection of viruses from respiratory samples is also affected by the time between symptom onset and specimen collection. Respiratory viruses are more likely to be detected when specimens are collected soon after symptom onset, as viral loads are generally higher early in the illness. The quality of sample collection is especially important in respiratory tract infection and training in sampling is recommended. Self-collected mid-turbinate nasal swabs may be considered to reduce turnaround times, although data on the sensitivity and specificity of testing using this approach are awaited.[19]

Antigen detection-based rapid influenza diagnostic tests (RIDTs) are simple to perform and interpret, but have limited sensitivity and specificity in detecting influenza virus, particularly when influenza activity is low or for novel influenza subtypes.[20] Although viral culture remains the gold standard for diagnosis, NATs are predominantly used given their increased sensitivity, specificity, breadth and reduced turnaround time to pathogen detection. Multiplex polymerase chain reaction assays allow the simultaneous detection of different respiratory viruses and some assays also contain bacterial targets.

Antiviral therapy for influenza virus infection should be initiated within 48 hours of symptom onset. However, hospitalised patients (including pregnant women) may benefit from antiviral therapy even when commenced after 48 hours. A four-fold increase in the risk of ICU admission or death was noted when the institution of oseltamivir was delayed beyond 48 hours after initial presentation.[21] Empirical antiviral therapy should not be delayed if influenza is suspected before laboratory confirmation of infection. Despite the benefits of oseltamivir (a category B1 medication in pregnancy), only 50–81 per cent of hospitalised pregnant women received this medication during the influenza pandemic of 2009.[7,21,22] There is reluctance among pregnant women to use oseltamivir despite available post-marketing data suggesting its safety during pregnancy and the benefits outweighing the potential risks to the fetus.[23] Women who are up to two weeks postpartum with suspected or confirmed influenza should also be treated with antiviral therapy.[24]

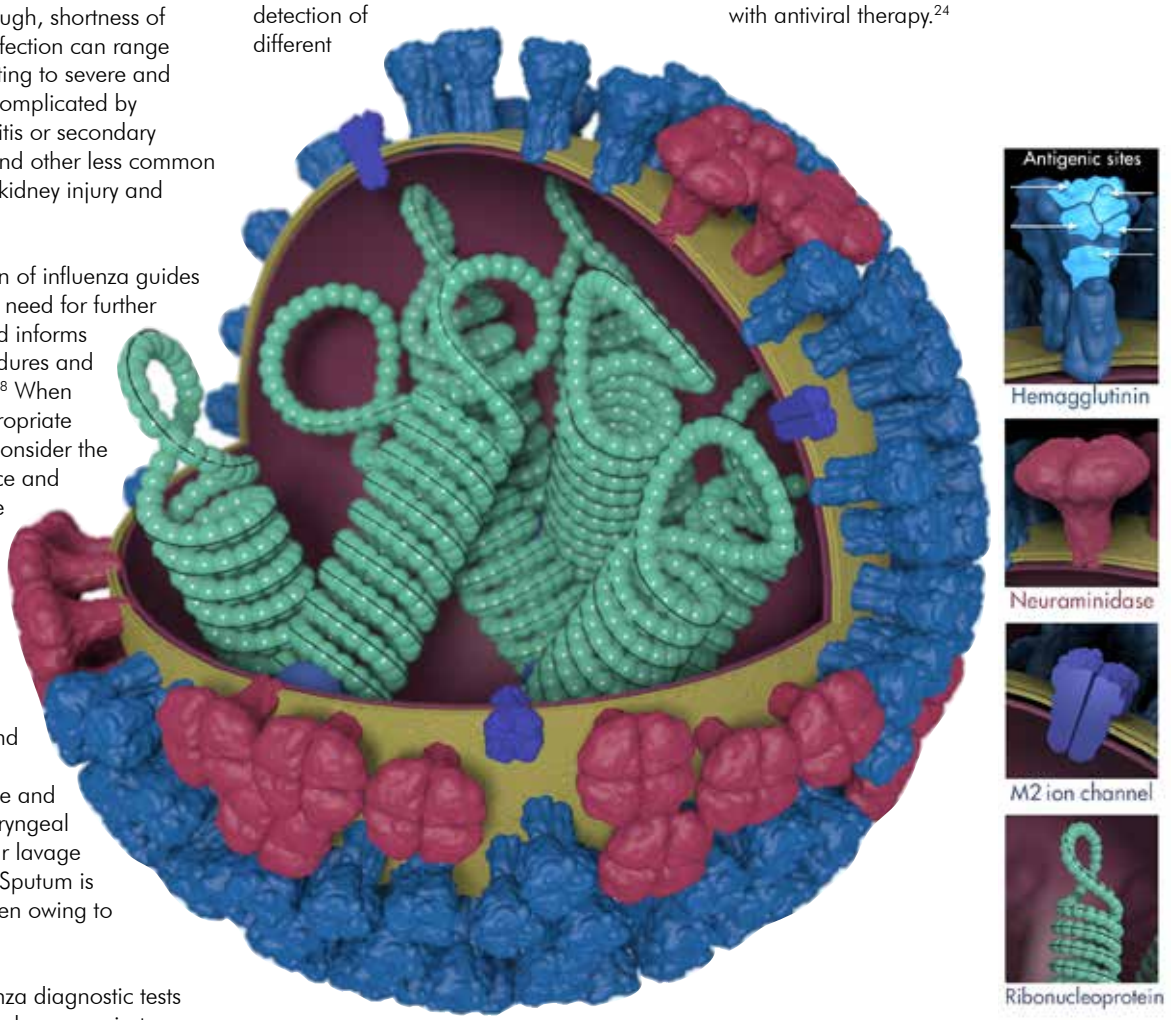

Figure 1. Influenza virus, illustrating the surface glycoproteins haemagglutinin and neuraminidase. Illustration courtesy of Dan Higgins, CDC Public Health Image Library.

Influenza vaccination is the only proven method to prevent influenza virus infection and is recommended for all pregnant women. Furthermore, it protects infants aged less than six months, in whom influenza vaccination in contraindicated.[25,26] Influenza vaccines may be administered an any time during pregnancy, before or during the influenza season. No significant long-term side effects (teratogenic, carcinogenic or neurologic) have been shown in pregnant women receiving the influenza vaccine during the first trimester[3] and would not be expected from a killed vaccine. A cohort of 6989 infants exposed to an adjuvanted influenza A(H1N1)pdm09 vaccine during pregnancy was not associated with increased risk of major birth defects, preterm birth or fetal growth restriction.[27] However, the uptake of the vaccine in pregnant women, even in the later stages of pregnancy is universally poor, despite evidence of significantly increased morbidity and mortality from influenza infection.[7] A recent Australian study also revealed that one-third of general practitioners did not believe influenza infection to be a significant risk to mother or baby and more than half had significant concerns about the safety of influenza vaccination during pregnancy.[28]

In conclusion, influenza virus infection during pregnancy causes significant morbidity and mortality. While further understanding of the pathogenesis of infection during pregnancy may help identify potential targets for therapies, vaccination is safe and effective and should be prioritised in this at-risk group to prevent infection.

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Dengue in Australia: the key points

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Dengue is responsible for upwards of 50 million infections per year worldwide; however, given that asymptomatic infection is possible, the true incidence is thought to be far higher. The virus is emerging or re-emerging in many regions of the world, including Australia, where episodic outbreaks occur in North Queensland. With a changing future climate, household water storage and mosquito distribution could affect outbreak frequency and the geographic distribution of this virus.

Virology

Dengue viruses (DENV) are enveloped viruses in the family *Flaviviridae*; genus Flavivirus. The genome is positive-sense, single-stranded RNA, which encodes seven non-structural proteins (including NS1, which is used for laboratory testing – see below) and three structural proteins.[1,2] There are four DENV serotypes (DENV-1, DENV-2, DENV-3 and DENV-4).[3] A fifth DENV type was discovered in samples collected during a dengue outbreak in Sarawak, Malaysia, in 2007; however, its transmission cycle is not believed to be sustained in humans.[4]

Transmission

DENV is transmitted via the bite of infected mosquitoes, predominantly *Aedes aegypti*, although *Aedes albopictus* also has the potential to carry DENV. The virus is maintained in a human-mosquito-human (urban) transmission cycle.[1,2] There is the chance of non-vector modes of transmission, including through needle-stick injury[5], transplantation[6] and transfusion of blood components.[7] Vertical transmission may also be possible during pregnancy or at birth; infection via such routes does not appear to result in long-term sequelae and there appears to be no association between the severity of disease in the mother and disease in the newborn.[8-11] DENV has been detected in the breastmilk of an acutely infected mother, suggesting that this may be a possible additional route of DENV transmission from mother to child.[12]

Epidemiology

According to the World Health Organization (WHO), more than 40 per cent of the world's population are at risk of dengue fever, with 50–100 million dengue infections occurring worldwide each year. A recent study re-evaluating the global impact of dengue estimated there to be 390 million infections per year (more than three times the WHO estimate).[13] Although dengue infection is traditionally more common in children, increasing numbers of cases in adults have resulted in more pregnant women being infected.[14] Dengue is endemic in tropical and sub-tropical countries, owing to continual circulation of the virus within an established mosquito population. More than 100 countries are endemic for dengue, including those in Africa, the Americas, the Eastern Mediterranean, South-East Asia and the Western Pacific. In Australia, dengue is not considered endemic; rather, it is episodic in North Queensland, owing to the presence of the primary vector: *Ae. aegypti*. Regular outbreaks occur seasonally in North Queensland.[15,16] One of the largest epidemics in at least 50 years occurred in 2008–09, affecting a significant proportion of North Queensland, totalling more than 1000 clinical cases[15,17] and, in 2013, this region experienced another outbreak, with approximately 200 confirmed cases.[18] There are a number of factors, such as changes in climate and human behaviour, that suggest that DENV might spread farther in Queensland and indeed to other parts of Australia.[19-21]

Clinical features

Infection can result in dengue fever (DF), dengue haemorrhagic fever (DHF), dengue shock syndrome (DSS), a range of intermediate responses or no clinical response at all.[3] Symptoms may include severe headache, severe joint and muscle pain, retro-orbital pain, nausea and vomiting.[3] Life-long immunity to infection occurs, but it is specific for the DENV serotype (cross protection between types persists only for several months). More severe symptoms (DHF, DSS) have been associated with secondary infection with a differing DENV serotype, which can be fatal.[3] In pregnant women, dengue infection may result in an acute febrile illness and there is a greater risk of pre-eclampsia, preterm labour and a low birthweight baby.[22] Most cases of DF infection in pregnancy result in no serious harm to the mother or baby; however, women who contract DF in early or late pregnancy tend to have a poorer prognosis.[14] Severe thrombocytopenia (platelet count of $<50\,000$ cell/mm^3) was observed in 79 per

Summary
Dengue has clearly emerged as a public health issue in many countries, including Australia. Given the likely increase in dengue transmission with climate change, this virus may affect more Australians in the future. As dengue infection during pregnancy may be associated with a poorer prognosis for both the mother and child, it is recommended that the Australian obstetric community be aware of such complications in order for them to be managed accordingly.

cent of a cohort of pregnant women with dengue in India, which included women in the second trimester.[14] However, many of these women had an uneventful course of infection, were treated conservatively and discharged.[14] Dengue infection in the neonate can range from an asymptomatic or mild disease, to DHF or DSS[11] and passively transferred antibodies, such as in breastmilk from an infected mother, may influence the clinical picture.

Case definition

In Australia, dengue is nationally notifiable, with both confirmed and probable cases requiring notification. A confirmed case requires laboratory definitive evidence (isolation of virus; detection through nucleic acid testing; or detection of DENV NS1 antigen in blood; DENV IgG seroconversion; an increase in DENV antibody level; or the detection of DENV IgM in cerebrospinal fluid, in the absence of IgM to other flaviviruses) and clinical evidence (a clinically compatible illness for example, fever, headache, arthralgia, myalgia, rash, nausea, vomiting and so forth).[23] A probable case requires laboratory suggestive evidence (detection of DENV IgM in blood) and clinical evidence as well as epidemiological evidence (a plausible explanation, for instance travel to an area endemic for dengue or exposure in Australia where local transmission has occurred).[23] Delay in notification is an important factor influencing outbreak duration in Australia[15], highlighting the importance of a timely diagnosis and of our notification system.

Treatment and prevention

There are no specific antiviral drugs available for the treatment of dengue infection. Treatment is dependent on symptoms and involves their management. For DF, this usually involves hydration and pain control (paracetamol, codeine or other agents that are not nonsteroidal anti-inflammatory agents). Hospitalisation and additional treatments are often required for DHF or DSS, including IV hydration, blood and/or platelet transfusions, blood pressure support and other intensive-care measures. Studies suggest that during pregnancy most cases require only conservative treatment unless there are complications[14,24], and platelet transfusion is only needed for women in labour or with a bleeding disorder.[14] There is no vaccine available, despite work in the area for a number of years. There are a number of candidate vaccines in the preclinical or clinical states of evaluation, with additional candidates in the research phase of development.[25] Some challenges faced by vaccine developers include the need to protect against all serotypes in naïve as well as previously immune individuals as well as the requirement to induce life-long protection against infection with all serotypes.[25] Prevention therefore currently relies on preventing mosquito bites and/or the control of the mosquito vector itself.

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Parvovirus infection in pregnancy

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Parvovirus – also known as 'slapped cheek syndrome' or 'fifth disease' – is a common viral infection that often affects children and those in close association, such as early years teachers. Outside of pregnancy it is a mild disease with few sequelae. However, parvovirus infection in pregnancy can result in miscarriage, fetal anaemia, hydrops or stillbirth. It is caused by Parvovirus B19 a small, single-stranded DNA virus that affects only humans. It is described as genotype 1 of the Erythrovirus genus belonging to the *Parvoviridae* family. The name implies multiple parvovirus types, but stems from the initial discovery of the virus when screening donor blood for Hepatitis B it was found on sample 19 in panel B. The other two genotypes (2 and 3) are found less commonly in the USA and Europe, but are more common in those who are immunosuppressed. Genotype 3 is typically more common in Sub-Saharan Africa and South America although it does appear to be spreading.[1] Parvovirus B19 will be considered more closely in this review.

Incidence and transmission

The incidence of Parvovirus B19 antibody presence increases with age. In a study that examined the serum of more than 2000 participants, more than 85 per cent of people over the age of 70 tested positive for the IgG.[2] Most infection seems to occur during the school years as 50–60 per cent of these children were already IgG positive.

Outbreaks have been reported as occurring in four-year cycles, with two years of epidemic followed by two years of endemic.[3] The nonspecific signs and symptoms of this infection may influence under-diagnosing and reporting, however.

Transmission occurs via three routes. The most common is respiratory, with the virus present in both respiratory secretions and saliva. This route is likely to be responsible for transmission rates of 50 per cent in household contacts. Haematogenous transmission is also possible. In New Zealand there is a warning attached to Prothrombinex™-VF as there have been rare cases of transmission via similar products. For the obstetrician, the route of transmission of most interest is vertical. The rate of vertical transmission in a woman with acute parvovirus infection is 50 per cent. This can result in inhibition of erythropoiesis and stimulation of apoptosis, leading to fetal anaemia, hydrops and fetal demise. Fetal thrombocytopenia is also reported.[4]

Time course of infection

Viraemia is typically present six days after exposure and lasts for around a week. As people are contagious before they are symptomatic, containing the spread of disease is not easily done. The development of rash marks the end of the infectious period, usually one-to-two weeks after infection.

Clinical manifestations

Infection is asymptomatic in 25 per cent of people. It produces nonspecific symptoms of fever, muscle pain and malaise in another 50 per cent. The remaining 25 per cent show more specific disease manifestations: including erythema infectiosum, a febrile illness associated with rash, arthropathy, transient aplastic crisis and red blood cell aplasia. The initial phase of infection in erythema infectiosum consists of around a week of non-specific symptoms, which can include fever, malaise, diarrhoea, headache and nausea. The classic slapped cheek rash then occurs and may be followed by a lace-like rash over the trunk and limbs, typically seen one-to-four days later. This is common in children.

Arthropathy occurs mainly in adult women and is associated with rash in 75 per cent of cases, although the appearance is not always as characteristic as it is in children. The symptoms can last for around three weeks; however, there are no destructive bony effects.

Transient aplastic crisis is common in those with pre-existing haematological abnormalities, such as sickle cell disease or iron deficiency anaemia. These patients present with symptoms of anaemia, with haemoglobin levels around 30 per cent lower than normal. Transfusion can be used if necessary, but the effects of infection are self-limiting, usually lasting up to three weeks.

Parvovirus B19 in pregnancy

Incidence of acute infection in pregnancy has been reported as two to four per cent.[5,6,7] There is no role for routine screening in a low-risk population. Although childcare workers are at an increased risk of exposure, the Australasian Society for Infectious Diseases does not recommend these women stop working as the overall risk of infection is similar to those exposed in the general community.[5]

The risk of vertical transmission is 50 per cent.[8] Infection between eight and 20 weeks poses the greatest risk to the fetus. When vertical transmission occurs, fetal disease manifestation usually presents from two weeks post-infection with 93 per cent being present by eight weeks. Up to a quarter of

fetuses will develop anaemia, some of which will spontaneously resolve, however up to 12 per cent develop fetal hydrops.[9] This is thought to be owing to both high output cardiac failure secondary to anaemia, but also direct myocardial injury following infection of myocardial cells. Death occurs in five to ten per cent of infected fetuses.[9] This means that up to five per cent of fetuses will die when maternal infection is present. Although some case reports suggest association between infection and congenital abnormality, there is no real evidence Parvovirus B19 is a teratogen.[8] There is also no evidence that the virus is directly responsible for poor long-term neurological function.

Diagnosis

Diagnosis of past infection is represented by positive IgG with negative IgM. A positive IgM result can be seen between ten days and three months post exposure and suggests acute infection. The sensitivity of the radioimmunoassay and enzyme-linked immunoassay tests is 80–90 per cent. Polymerase chain reaction testing is better at picking up very small amounts of B19 DNA and can be reserved for women with a clear history of exposure and a negative IgM and for diagnosing fetal infection from amniotic fluid samples. Sampling of amniotic fluid is not necessary, but if an amniocentesis was being performed for other reasons, such as karyotyping, the test could be done for confirmation.

Management

There is no specific treatment for Parvovirus B19; however, some of the effects of the virus can be treated. Following confirmation of acute infection by seroconversion in the mother, there should be monitoring with ultrasound for evidence of fetal anaemia and hydrops. This monitoring should start four weeks post conversion/infection and continue for up to 12 weeks, as this is the window of greatest risk to the fetus. Ultrasound may indicate signs of severe anaemia and hydrops, including skin oedema, ascites and pleural and pulmonary oedema.

Diagnosis of fetal anaemia should be suspected when assessment of the middle cerebral artery Doppler peak systolic velocity (MCA PSV) is greater than 1.5MoM (multiples of the mean). Where severe anaemia is suspected (MCA PSV >1.5 MoM), a fetal blood sample should be performed to quantify this and also to check for platelets as thrombocytopenia can occur concurrently.[4] Cordocentesis in these cases can lead to fetal exsanguination.

Identification of fetal hydrops or suspected anaemia should trigger urgent referral to a fetal medicine specialist unit able to undertake in utero transfusion. If the fetus is near term, delivery can be considered. Intrauterine transfusion is not without risk; however, studies suggest that mortality is higher in those who do not undergo transfusion than those who do. One study of 539 cases of Parvovirus B19-induced hydrops reported mortality rates of six per cent in the fetuses who underwent transfusion and 30 per cent in those that did not. A third of the fetuses with hydrops had spontaneous resolution.[9]

Where fetal hydrops is present, delivery should be at a hospital with a level-3 neonatal intensive care unit. A specialist paediatrician should attend the delivery as intubation and fluid drainage may be necessary. The baby might require ventilation and possibly other support, such as inotropes. A haemoglobin and platelet count should be taken on day 1 and appropriate transfusion given where necessary.

There is no risk of recurrence to the affected mother or child.

Summary

Parvovirus B19 is a DNA virus with moderate rates of transmission from individuals who may be asymptomatic. Around 30–40 per cent of pregnant women are not immune and are therefore at risk. Although rare, the consequences of fetal hydrops and death are devastating and any suspected exposure must be investigated so that appropriate fetal monitoring and treatment may be arranged.

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Rubella and varicella in pregnancy

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As vaccination coverage varies in different countries and global travel increases, awareness of vaccine-preventable diseases continues to be important. In 2011–12, there were 36 cases of rubella and one notified case of congenital rubella syndrome in Australia.[1] Over the same period, there were 805 hospitalisations for chickenpox. Rubella and varicella are both highly contagious and can have severe consequences in the antenatal and perinatal setting. An excellent resource is the Australian Society of Infectious Diseases (ASID) Perinatal Guidelines.[2]

Rubella

Worldwide, outbreaks of rubella have been described, with 29 cases in Vietnam in January already reported this year.[3,4] Most infections are clinically apparent; after an incubation of 14–23 days, a cephalocaudal rash occurs in 75 per cent of cases and lasts two to seven days. Subclinical infections may be more common with secondary infection or vaccine failure.[5] Less than five per cent of pregnant women are not immune at antenatal screening, although the protective antibody level is debatable.[6] A small proportion of women are affected by reinfection and congenital rubella syndrome in this context has been reported.[5,7] Antibody levels decrease over time and this may be particularly so in those vaccinated with the Cendehill strain prior to 1986.[8] The WHO-recommended cut off for evidence of immunity is a rubella-specific IgG level above 10 IU/mL, and our immunisation guidelines recommend re-immunising if standard assays do not demonstrate evidence of current immunity.[9]

Diagnosis of maternal infection

Rubella testing in pregnancy should only be performed where there is a history of a rubella-like illness (fever, rash, arthralgia) or contact with confirmed rubella.[2,10] In the first trimester, a pregnant woman should undergo testing even if she previously had a positive rubella IgG. If contact occurs in the second or third trimester, further testing is not necessary. A diagnosis is suggested by either antibody seroconversion or a four-fold rise in the IgG titre. Serology should be collected as soon as possible after contact or the onset of rash and repeated 10–14 days later. The diagnosis can be confirmed via nucleic acid testing or culture (on nasal specimens, blood and urine), but neither is widely available. As with all serology, false positive results and cross-reactivity occur and so caution is advised in counselling the mother on this basis alone.[10]

Management of suspected infection

The risk of fetal infection is low in maternal re-infection; less than five per cent overall and rare after 12 weeks gestation. There is no specific therapy for the mother, as rubella specific immunoglobulin is not effective as post-exposure prophylaxis and normal human immunoglobulin is not indicated.[11,12]

In primary maternal infection, the risk of fetal infection varies with gestation. The highest risk is in the first trimester with organogenesis, when the rate is 80–90 per cent with a similar risk of congenital defects.[13] At 13–16 weeks gestation the risk of fetal infection is around 50 per cent, with around one-third complicated by congenital defects, primarily deafness.[13] Thereafter, congenital defects are rare.[5,11]

Termination should be considered in the first trimester of pregnancy. Fetal testing may be performed via rubella polymerase chain reaction (PCR), rubella culture and fetal IgM on chorionic villus sampling or amniocentesis in the second trimester, at least six weeks after maternal infection. Although the specificity of PCR is excellent, there can be difficulties with interpretation, as PCR may be positive from contamination of the specimen with maternal tissue, and false negative fetal IgM is common until late in pregnancy.[14]

The infant at risk of rubella infection

Congenital rubella syndrome can be devastating, with deafness, cataracts, micropthalmia and heart defects (patent ductus arteriosus). After birth, the infant may continue to shed rubella virus for many months and, so, should be looked after only by individuals who have evidence of immunity to rubella. The infant should undergo testing for rubella via serology (IgM), PCR and culture of urine and throat specimens (if available).

Clinical features of congenital rubella syndrome can include:

- sensorineural hearing loss (60–75 per cent);
- opthalmological (10–25 per cent) – cataracts, micropthalmos, retinopathy, glaucoma, strabismus, cloudy cornea;
- CNS (10–25 per cent) – developmental delay, mental retardation, microcephaly;
- CVS (10–20 per cent) – patent ductus arteriosus, pulmonary artery stenosis, pulmonary stenosis; and/or
- growth retardation, haematological

and gastrointestinal abnormalities, pneumonitis and osteitis.

Late manifestations include epilepsy, tooth defects, insulin-dependent diabetes mellitus (50 times the rate in the general population), thyroid dysfunction and panencephalitis.[11]

In the absence of these features, but with a positive IgM (and/or PCR), the infant is infected, but asymptomatic. These infants should also be isolated from potentially pregnant female contacts, and in droplet and contact precautions while in hospital. Breastfeeding can be continued.

Varicella

Varicella infection is highly contagious and has an incubation period of 10–21 days. It is infectious from two days before the rash until lesions have crusted over. In adults, clinical findings strongly suggest the diagnosis and this is confirmed on nucleic acid testing and/or immunofluorescence. Serology is useful in establishing risk in the antepartum period and, if negative, immunisation should be offered postpartum. Fetal infection occurs in 10–15 per cent of cases of chickenpox, is usually transient and most commonly manifests as shingles in the infant.[13] Chickenpox in the first half of pregnancy is complicated by fetal varicella syndrome in two to three per cent of pregnancies. Congenital varicella syndrome is characterised by microcephaly, low IQ, convulsions, dermatomal skin scarring and ipsilateral limb hypoplasia.

Exposure during pregnancy

Exposure to varicella during pregnancy is a common problem encountered in obstetric, general and infectious diseases practice, although it has become less so since the introduction of routine childhood immunisation. Women who have had significant exposure (living with someone with active chickenpox or herpes zoster, or face-to-face contact for at least five minutes) should be evaluated.[2]

If the mother has had chickenpox previously or she has been vaccinated, nothing further is needed. If her history is uncertain and serology is negative or unavailable within 96 hours of exposure, she should be given varicella zoster immunoglobulin (ZIG). ZIG is most effective within 48 hours, but is not effective after rash onset.[13] After the 96-hour mark, post-exposure prophylaxis may be considered for women in the second half of pregnancy who also have underlying lung disease, are immunocompromised or who smoke. This is owing to an increased risk of varicella pneumonia in this subset of women.

Management during pregnancy

Oral acyclovir is effective if started less than 24 hours after the onset of chickenpox rash. Complicated chickenpox is characterised by respiratory, haemorrhagic or neurological complications, new lesions or persistent fever after six days. Complications or infection in immunocompromised women should be treated with intravenous acyclovir.

The infant at risk of varicella

Although fetal varicella syndrome (FVS) in the first trimester is rare, intrauterine diagnosis is often requested. Major abnormalities can usually be detected by serial ultrasound examination in the second trimester. If abnormalities are detected, the diagnosis can be confirmed by amniotic fluid PCR. In the absence of gross abnormalities, PCR performed at least six weeks after maternal infection has a high negative predictive value.[15] A positive result indicates fetal infection, not necessarily damage. An ultrasound is required to assess the impact on the fetus, if any.

In the perinatal period, the risk of infection varies with the timing to delivery, as it can be acquired in utero or in transition through the birth canal. Chickenpox that occurs more than one week before delivery presents very little risk; very preterm <28 weeks or very low birthweight <1kg infants are treated with intravenous acyclovir nonetheless. If it occurs between two and 28 days after delivery, varicella immune globulin should be given to preterm and very low birthweight infants. The greatest risk is in the context of infection between seven days before and two days after delivery, in which instance varicella zoster immune globulin should be given immediately.

Term infants exposed to chickenpox require no specific action if their mothers are immune. In the absence of demonstrated immunity, ZIG should be given, ideally within 96 hours of exposure. They should then be isolated between days seven to 21 after exposure.

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Sim one, do one, teach one: the past, present and future of simulation

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Recent articles in this magazine have highlighted the plight of registrars' surgical skills training. Stories of a bygone era of 100-hour working weeks, where logbooks were futile when operating day and night, ring loudly in the ears of today's Trainees who struggle to accumulate the numbers to become a confident surgeon. RANZCOG training is evolving in an attempt to address the issue, but ultimately all registrars must obtain surgical competency across a broad range of procedures, with fewer cases per Trainee. New methods of surgical training are needed in order to adapt to a world influenced by safe working hours, a large number of Trainees and reduced surgical cases secondary to the advancement of medical therapies. The use of simulation will be a vital tool to ensure the Trainees of the future obtain the skills necessary to make them a competent specialist.

Theory of simulation

It is helpful to reflect on how technical skills are acquired. The Fitts/Anderson model describes a progression though cognitive, associative and autonomous phases of learning (see Table 1).[1] Traditionally, a Trainee is like an apprentice, observing senior surgeons and operating under their guidance until sufficient mastery of a procedure is achieved (the associative phase). The autonomous phase is only reached after unsupervised repetition of procedures. This model served surgical training well during an in an era of mostly open surgical procedures, a large volume of cases and an acceptance of a degree of error during training.

Simulation training supports a Trainee's progression through the cognitive, associative and autonomous phases in a simulated procedure, in a safe environment. This allows consistent, accurate and automatic performance of tasks prior to live surgery. While this does not mean that a Trainee can then perform live surgery without supervision, it creates a 'pre-trained novice'[2], who now possesses the ability to spare attention to comprehend his or her supervisor's instructions and gain a superior learning experience from each live surgery.

History of simulation

While the understanding of the neuropsychology of skill acquisition is recent, medical practitioners have understood the value of simulated practice for centuries. Descriptions of the early use of simulation for medical education make fascinating (and often morbid) reading, detailing anatomical models dating back to the 11th century and birthing simulators from as long as 250 years ago.[3] Madame du Coudray, a French midwife, revolutionised obstetric care in 18th century France using an intricate and adaptable birthing simulator. Travelling the countryside on her bicycle, she taught illiterate French peasant girls how to deal with all manner of obstetric emergencies using her 'machine'. Further lessons came from Vienna in the 19th century, when a move away from artificial simulators to cadavers for simulation resulted in a ten-fold increase in maternal mortality (subsequently expanding the availability of cadaveric models) until the association of puerperal fever and hand hygiene was finally proved.

Evidence for simulation

There is ample evidence that skills learned in simulation transfer to patient care, with improved performance demonstrated over a range of procedures, including: CPR, laparoscopic surgery, endovascular procedures, endoscopy and even cardiac auscultation. Specifically in our specialty, team training for obstetric emergencies has reduced rates of brachial plexus injuries and hypoxic-ischemic encephalopathy[4,5], while laparoscopic simulation training has been shown to improve performance in laparoscopic gynaecological surgery. Larsen in 2009[6] randomised junior trainees learning laparoscopy to simulator training versus usual training. When performing a live salpingectomy, the simulator-trained group completed the salpingectomy in half the time (12 versus 24 minutes), and achieved technical proficiency scores equivalent to surgeons with experience of

Table 1. Fitts/Anderson model of stages of skill acquisition with examples.

Phase	Processes	Example
Cognitive	Understands/problem-solves the mechanics of the task by acquiring knowledge and watching demonstrations Performs the task slowly and deliberately Thinks through or verbalises task steps during execution	Learns that to rotate tip of laparoscopic instrument you turn the rotation knob at handle Has to consciously think through this before or as doing it
Associative	Begin to develop association between the cognitive component and the psychomotor tasks Performs the task with greater efficiency and less error No longer thinks through steps or verbalises during execution	Begins to turn rotation knob on instrument when wants to rotate tip with less conscious thought Still somewhat inefficient
Autonomous	Psychomotor movements are automated Cognitive involvement is eliminated May lose ability to verbalise or describe steps	Automatically and efficiently turns rotation knob when wants to rotate tip of instrument

20–50 laparoscopies, as opposed to the control group whose scores equated to less than five procedures. This is a remarkable demonstration of the power of simulation training. Other randomised controlled trials have had shown similar improvements with simulator training in laparoscopic tubal sterilisation.[7,8]

Integrating simulation into training

Despite the evidence for use of simulation, uptake remains surprisingly patchy and the reasons are unclear. In the implementation of a surgical simulation curriculum in the US, identified barriers include lack of protected time, lack of personnel, associated costs and work hours restrictions.[9] Attitudes may also play a role, with one study suggesting that while 92 per cent of surgical trainees believed simulated laparoscopic skills transfer to the operating theatre, only 57 per cent agreed that laparoscopic simulator proficiency should be demonstrated prior to operating theatre exposure.[10] The discrepancy between belief and action is peculiar. It is interesting to ponder how the general public may respond to a question regarding the necessity for trainee surgeons to demonstrate simulation proficiency prior to operating on patients. Perhaps the response may be: 'What? Do you mean they don't have to do that already?'

In contemplating a future simulation curriculum, a successful design process should critically consider all phases of the trainee's skill acquisition. There should be a cognitive component, where students can understand the context of psychomotor skills they are about to learn. For surgical training, this may include relevant aspects of instrumentation, anatomy, procedural steps, errors and teamwork considerations. Trainees should be able to rehearse psychomotor tasks on a validated simulator and receive feedback on their progress using clearly defined performance criteria. A program should have elements of deliberate practice, distributed practice and variability of practice and should continue until proficiency is demonstrated. A certain amount of 'overtraining' can also be useful. Feedback is a vital part of trainees improving and maintaining enthusiasm.

It should not be assumed that the provision of the tools for a simulation program is enough to guarantee success. Trainees need to be motivated to participate, especially considering the multiple demands on a trainee's time. Mandated, protected and supervised time to train provides the external motivation for trainees to engage in a simulation curriculum. Compulsory proficiency before live operating theatre performance may prove a strong motivator for learning, perhaps furthered by some healthy competition with peers.

In developing simulation curricula, it is also important to consider the ease of dissemination and adoption. It is no wonder that the American College of Surgeons had difficulty in implementing their simulation curriculum given its cost of more than US$30 000 per student.[11] Operating on live animals and cadavers undoubtedly provides a premium learning opportunity, but the costs are prohibitive if considering widespread implementation. These models are perhaps best reserved for advanced training.

Where to now?

We know that evidence exists to support simulation. Some elements of simulation training are already occurring and understanding what is happening is the first step towards integrating simulation in a united approach. The international simulation community has recently developed a framework for curriculum development.[12] Development of a curriculum will require significant input from all regions, and perhaps should initially focus on basic procedures for junior trainees. Prior to developing a curriculum, we first need to understand the likely economic, organisational and psychological barriers to widespread acceptance and implementation. Implementation will require a significant investment of time, energy (and money). It will also be vital at the outset to have in place a rigorous evaluation process to ensure that we are getting it right.

The perfect way to train is an enigma, however, simulation is a key strategy to ensure our patients stay safe while we train tomorrow's specialist. In 2003 Ziv[13] stated, with respect to medical education, 'Although such risks [patient harm] are usually considered an unavoidable concomitant of training, the harm caused is ethically tolerable only when minimised to the degree possible by medical pedagogy.' More than ten years later, with knowledge that the old training model isn't working, simulation is the 'ethical imperative'. We must continue to assess, improve and evaluate our training curricula in our role as the trainers of the specialists of the future and guardians of the highest standard of care for our patients.

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Case report

A heterotopic or secondary abdominal pregnancy?

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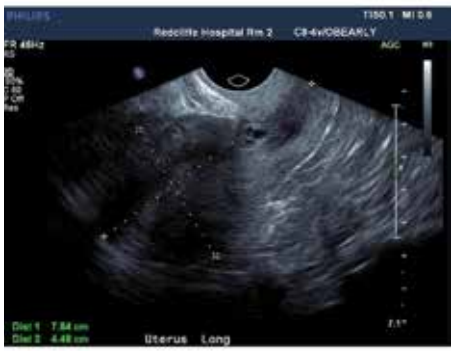

Figure 1. Ms Y's ultrasound findings consistent with a caesarean scar ectopic.

Case report

Ms Y, a 30-year-old gravida 2 para 1 (lower segment caesarean section for failure to progress), presented to the emergency department (ED) with right iliac fossa pain, ten days of amenorrhoea and a positive beta-HCG (720IU/L). Ultrasound revealed a 17mm mass in the right adnexa and a small amount of free fluid in the pelvis. She underwent a laparoscopic right salpingectomy for an ectopic pregnancy. A moderate haemoperitoneum was noted intra-operatively.

Twenty days post salpingectomy, Ms Y presented to her GP with further right iliac fossa pain, but no PV bleeding. Her beta-HCG was 980IU/L and rose to 1200IU/L after 48 hours, upon which she was referred back to the ED. Review of histopathology from Ms Y's recent salpingectomy confirmed a tubal gestation. Ms Y denied any sexual intercourse since discharge. Subsequent transvaginal ultrasound revealed cystic structures within her caesarean scar that were suspicious of a caesarean scar ectopic.

Ms Y was transferred to a tertiary centre for further imaging and management. A second ultrasound confirmed the diagnosis of a caesarean scar ectopic. She was treated with intravenous methotrexate upon which her beta-HCG dropped appropriately.

Discussion

Ms Y presents an unusual case of a caesarean scar ectopic with uncertain aetiology. Two hypotheses have been proposed to explain her clinical course. Firstly, an early secondary abdominal pregnancy post spontaneous tubal abortion and, secondly, a heterotopic pregnancy with two ectopic gestations.

Secondary abdominal pregnancies are very uncommon.[1] They have been reported following a tubal ectopic rupture, removal or abortion and, very rarely, later in pregnancy, following uterine rupture.[2] It is hypothesised in this case that Ms Y's right tubal pregnancy miscarried into the abdomen and some of this tissue implanted into her caesarean scar, resulting in the caesarean scar ectopic. No case reports of secondary abdominal pregnancies resulting in caesarean scar ectopics could be found in the literature.

Heterotopic pregnancies, where two simultaneous gestations implant at different sites, occur in one in 30 000 spontaneous pregnancies.[3] This incidence is significantly increased with artificial reproductive technology (ART) to approximately two per cent of ART pregnancies.[3] The most common form of a heterotopic pregnancy is with one intrauterine gestation and one extrauterine gestation (most commonly in the fallopian tube). No case reports of simultaneous tubal and caesarean scar ectopic gestations could be found in the literature.

Conclusion

The incidence of caesarean scar ectopics is increasing with rising caesarean rates. It is reported to occur in approximately one in 2000 pregnancies where the woman has had a previous caesarean section.[4] There is no clear management guideline for a caesarean scar ectopic. Treatment options are aimed at minimising complications and preserving fertility: methotrexate is commonly used.[5]

It is not routine to re-test beta-HCG in women post laparoscopic removal of tubal ectopic pregnancies. However, with the rising incidence of heterotopic pregnancies and the risk of secondary abdominal pregnancies, one must ask whether it is wise to start doing so. A repeat beta-HCG assay could be considered in all women, particularly in women who have undergone ART or whose tubal ectopic has ruptured or aborted. Whether this should become routine is for the reader to decide.

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Journal Club

Had time to read the latest journals? Catch up on some recent O and G research by reading these mini-reviews by Dr Brett Daniels.

Non-invasive prenatal testing

The discovery of cell-free fetal DNA in maternal blood, in 1997, eventually led to the commercial non-invasive prenatal testing (NIPT) services available today. Initially seen as expensive and specialised, NIPT has fallen rapidly in cost and has become widely adopted for the prenatal detection of fetal aneuploidies. For example, in my private practice, the out-of-pocket cost of NIPT testing fell rapidly from $1500 at introduction to less than $600 at the time of writing.

Warsof et al review the impact of NIPT testing on prenatal screening and on the performance of invasive diagnostic procedures, such as chorionic villus sampling (CVS) and amniocentesis.[1] In terms of the rapid adoption of NIPT, the authors cite a 2011 study by Sayres et al that reported only 29 per cent of clinicians thought they would be using NIPT in their practice within five years. A study two years later reported that more than 90 per cent of fetal maternal medicine specialists were using NIPT in their clinical practice. Warsof et al report patients most value NIPT for the decreased risk of miscarriage compared to invasive testing, while doctors report greater accuracy compared to other screening tests as NIPT's most valuable feature.

It was expected the introduction of NIPT would reduce the number of other first trimester screening tests performed, particularly in high-risk women. Warsof et al confirm this, reporting that in high-risk women in the US, the rate of first trimester combined screening decreased by 50 per cent in the first year after the introduction of NIPT. A major impact of the introduction of NIPT has been a dramatic reduction in the number of invasive prenatal tests, such as amniocentesis and CVS. The review examines a number of studies, showing there was a large decrease in invasive testing following the introduction of NIPT, ranging from about 30–90 per cent. The reduction in the number of invasive tests is attractive to both doctors and patients, particularly with the concomitant reduction in procedure-related miscarriages. However, it should be noted NIPT is still considered a screening tool and requires confirmation with diagnostic testing. An unintended consequence of the reduction in the number of diagnostic tests performed is that individual practitioners may not have sufficient case numbers to maintain optimum skills and, therefore, testing may eventually be restricted to a small number of specialist centres. While NIPT testing has so far been recommended for pregnancies at high risk of genetic problems, the rapid adoption and falling costs of the testing may well mean that it is applied to low-risk women in the future.

1 Warsof SL, Larion S, et al. Overview of the Impact of Noninvasive Prenatal Testing on Diagnostic Procedures. *Prenatal Diagnosis.* 2015, DOI: 10.1002/pd.4601.

Postmenopausal urogenital symptoms

Following menopause, reduced oestrogen results in many women experiencing urogenital symptoms, including vaginal dryness, irritation, dyspareunia, overactive bladder and recurrent urinary tract infections. The terms currently used for this syndrome include atrophic vaginitis and vulvovaginal atrophy. However, these terms are thought by some to be inadequate; descriptive of the postmenopausal vulva and vagina without mentioning symptoms and with the term 'atrophy' having negative connotations for many women. A recent paper by the International Society for the Study of Women's Sexual Health (ISSWSH) and the North American Menopause Society (NAMS) reports the result of a consensus meeting that arrived at the new term of genitourinary syndrome of menopause (GSM). GSM includes the symptoms of genital dryness, decreased lubrication with sexual activity, dyspareunia, postcoital bleeding, decreased arousal, orgasm and desire, irritation/burning/itching of vulva or vagina, dysuria, urinary frequency and urgency. It also includes the signs of decreased vaginal elasticity and moisture, resorption of the labia minora, pallor and erythema, loss of vaginal rugae, prominence of the urethral meatus, introital retraction and recurrent urinary tract infections.[1]

The mainstay of treatment of GSM is topical vaginal oestrogen. Vaginal oestrogen creams or pessaries are well-tolerated, safe treatments that provide symptom relief to many women. Some women, however, find topical oestrogen difficult and/or unpleasant to use and may have concerns about cancer risk, although this concern is generally thought to be unfounded. For these women, alternative treatments may be desirable. Wurz et al describe the results for a new selective oestrogen receptor modulator (SERM), ospemifene, for the treatment of postmenopausal dyspareunia. Ospemifene exerts a strong oestrogen agonist effect on the vaginal epithelium with Phase III clinical trials showing that oral ospemifene significantly improved the vaginal maturation index and self-reported symptoms of dyspareunia and vaginal dryness compared to placebo. Long-term safety studies revealed that 60mg ospemifene given daily for 52 weeks was well tolerated and was not associated with any endometrial or breast-related safety concerns.[2] Ospemifene is not yet available in Australia or New Zealand, but lobbying for its introduction is currently underway, particularly among survivors of breast cancer, in whom topical oestrogen may be a concern.

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Q&a

For the broader *O&G Magazine* readership, balanced answers to those curly-yet-common questions in obstetrics and gynaecology.

Q *'My patient has cervical HPV and asks if she or her partner are at risk of throat cancer. What should I tell her?'*

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a Recently, many people have become aware of information in the media suggesting that there is a link between human papillomavirus (HPV), which might be transmitted by oral sex, and oropharyngeal cancer. Little is known about the natural history of oropharyngeal HPV, but it is an area of rapidly emerging new knowledge. In common with anogenital HPV-related disease, a viral aetiology for oropharyngeal cancer raises questions for the patient, their partner and health practitioners. Common concerns are how the virus is transmitted, whether there have been sexual partners outside of the couple and how to manage an ongoing sexual relationship. It is important to emphasise that a diagnosis of HPV-related cancer does not necessarily imply multiple sexual partners or other partners outside the relationship. There is no need to alter sexual activity with a stable partner, as sharing of HPV would have occurred long before the clinical appearance of the cancer.

Does HPV cause throat cancers?

HPV is now responsible for the majority of oropharyngeal squamous cell cancers (OSCC).[2,3,4] Smoking has traditionally been the most common cause of head and neck cancers. However, in the last 30 years the incidence of smoking-related head and neck cancer has declined in most countries. This has coincided with an increasing incidence of HPV as the aetiological factor in these cancers, including in New Zealand.[1] In the oropharynx (tonsils and base of tongue), up to 72 per cent of OSCC cases are now attributable to HPV.[2,3,4]

The latency after HPV infection is typically at least ten years and can be several decades. OSCC can present with throat symptoms and an ulcerated or non-ulcerated mass visible on oral examination. However, many patients have lateral cervical lymph node metastases at the time of diagnosis and, not infrequently, a neck mass is the only clinical finding at diagnosis. Therefore, HPV-related OSCC should be considered in any patient, particularly a man, presenting with a painless lateral neck mass. The prognosis for patients with HPV-related oropharyngeal cancer is much better than for those with HPV-negative, smoking-related oropharyngeal cancers.[9,10]

How common is throat cancer?

Not only is the proportion of OSCC cases that are HPV-positive rising, but the incidence of OSCC is also rising. OSCC is approximately four-times more common in men than in women.[1,4] In the US, the rate of OSCC in men (ten per 100 000) is now higher than the rate of cervical cancer in women (four to five per 100 000).[1] In New Zealand, the rate of OSCC in men in 2012 was four per 100 000 compared to a rate of cervical cancer in women of seven per 100 000 (statistics from New Zealand cancer registry).

Why is it more common in men?

The exact reason for this gender predilection is not clear; putative reasons are a greater viral load in the female genital tract and a greater immune response in women than in men.[8] The epidemiology that has been published does not differentiate between heterosexual men and men who have sex with men (MSM).

Does oral sex cause throat cancers?

Oral sex itself doesn't cause cancer, however, oral sex is strongly associated with oral HPV infection and increased odds of OSCC. Many people have oral sex, but few develop throat cancers. Between the ages of 15–44, 80 per cent of people have had oral sex, and so far it appears only a very small percentage of the population will develop throat cancers.

What are the risk factors for OSCC?

The HPV subtypes implicated in OSCC are similar to those involved in cervical cancer. HPV 16 is implicated in up to 90 per cent of HPV cases.[3,5] A strong correlation is seen between higher numbers of oral sexual partners and the development of OSCC, particularly with six or more lifetime sexual partners.[6,7] Other features of sexual behaviour, which are less strongly associated include younger age at sexual debut, history of genital warts or sexually transmitted infections, rare or non-use of condoms and oral-anal sex.[7]

Possible other co-factors are smoking, chewing tobacco, having a weakened immune system, poor oral hygiene and conditions causing chronic irritation to the throat. Chronic irritation of the throat may be caused by chemicals irritants such as alcohol or acid reflux, and chronic bacterial tonsillitis.

Is there a test for oral HPV?

There is no routine test to diagnose oral HPV and there is no recommended screening for it. As yet, there is no guidance on what the results of oral HPV DNA test mean or how to interpret this.

What about prevention?

In contrast to cervical cancer, no clinically apparent premalignant condition exists in the vast majority of patients. Similarly, there is no reliable laboratory screening test. Therefore, there is currently no indication for population screening for HPV-related head and neck disease.[11,12] This is an increasingly prevalent disease, however, and increased awareness of the disease among health professionals and the general population is to be encouraged. Limiting the number of sexual partners, delaying the onset of sexual activity and using barriers such as condoms and latex

dams while performing oral sex, may be expected to minimise the risk of developing HPV-related oropharyngeal cancer.

HPV vaccination holds great promise as a mechanism for preventing the development of benign and malignant head and neck HPV-related disease. Vaccination of both boys and girls prior to the onset of sexual activity is strongly recommended.[12]

What is the risk to partners?

In attempting to address this, it is important to put things in context and address some of the wider issues regarding HPV. The patient who is asking this question may be anxious that she will transmit HPV to her partner. It is important to explain that:

- More than likely, he already has been exposed to HPV. Sharing of HPV would have occurred long before the abnormal smear result or clinical appearance of a lesion.
- It is not possible to know how long ago or from whom HPV was acquired.
- Most sexually active people get HPV at some time in their lives, although most never know it.
- In a long-term relationship, HPV does not imply other sexual contacts and there is no need to alter sexual practice.
- In a new relationship, barrier protection could be considered, but one would normally encourage safe sex practices anyway in any new relationship.
- HPV virus can develop long periods of latency and then reactivate.
- Most individuals will become undetectable by DNA testing within one or two years.
- Most people who acquire HPV do not develop health problems from it.
- Partners of women with high-risk HPV (as opposed to low-risk types) can be made aware of the possibility of oropharyngeal cancer, even though the risk is low, and the possible clinical presentations.
- The risk of a male partner for throat cancer is really independent of the fact his partner has HPV. His risk of developing OSCC depends on whether the HPV is a high-risk type (in particular HPV 16) and his own lifetime risk factors such as smoking, lifetime number of sexual and oral sex partners, oral hygiene and conditions that cause chronic irritation.

While it is helpful to normalise a diagnosis of a viral sexually transmitted infection, it is important not to unintentionally be dismissive of the potential for psychological morbidity. The way to do this is to proactively provide information and education and address key concerns.

The website www.hpv.org.nz provides an excellent NZ-based resource for information for both health professionals and patients, including downloadable patient information, telephone and email counselling.

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Letters to the editor

Aldo Vacca remembered

As an obstetrics and gynaecology senior registrar in 1994 and 1995, at the Mater Hospital, Brisbane, I had the great pleasure and privilege of being trained by Dr Aldo Vacca. He was responsible for managing a very cohesive unit, where we all worked well together developing friendships that persist to this day. These were rekindled during the recent RCOG/RANZCOG meeting in Brisbane, where and when it was determined that we should honour Aldo's legacy in a more appropriate way than the recent article (*O&G Magazine* Vol 17 No 1 Autumn 2015 p55).

He was not motivated by money evidenced by the old, modest car he drove. His interest was in the safe care of mothers and safe delivery of babies. His passion, enthusiasm and immense skill in performing vacuum extraction were infective. It was impossible to contemplate performing an instrumental delivery by any other method. His reputation went before him. One of his former trainees, then working in London, described Aldo conveying that vacuum delivery was an art, not simply placing the cup somewhere near the fetal occiput and pulling. She was convinced that Aldo's epithet would be 'it [the flexion point] is always more posterior than you think'.

He was a great role model in how to be a labour ward consultant. He was always available, his office was on the labour ward and his door was always open. Nothing went past his watchful eye. He maintained that post vacuum delivery we must always check whether the cup had been placed on the flexion point and if not what sort of application had occurred. He ensured that we always checked the application point. Following an unsuccessful vacuum delivery we were encouraged to determine the reason.

> 'We remember his immense long-term vision for the future and his endeavours in designing his OmniCup '

We remember his immense long-term vision for the future and his endeavours in designing his OmniCup (Kiwi cup). Several of us auditioned its use to ensure that the cup could be easily used, regardless of hand/glove size. Two decades later, the realisation of his wish that this instrument be successfully and widely available has come to fruition.

Those of us trained by him at the Mater Hospital in Brisbane recall his reaction to being presented with the cartoon of his caricature (see below).

Seeing his wife Jan and his daughter continue his legacy and his teaching is brilliant. A fundraising symposium is being held in his memory at the RCOG in London, in September 2015. This has motivated us to request RANZCOG consider something similar.

Dr Aldo Vacca reacts with pleasure and surprise, having been presented by his colleagues with a framed cartoon featuring his caricature (photo taken in 1995).

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Honouring Aldo Vacca

We write to commend to the College fraternity the great clinician and innovator that our profession had in Dr Aldo Vacca AO. We were some of the lucky registrars to work alongside and to be trained by Aldo. He was committed to making us the best doctors we could be and we loved him dearly.

He was not only a master of obstetric intervention in the use of the vacuum cup, but also a doctor committed to evidence-based care while it was still in its early stages. He was warm and empathetic with his patients and showed, by example, that caring for pregnant women, simply and genuinely, in complex situations could be achieved by good communication, explanation and negotiation.

Aldo was a great initiator and knew, well ahead of his time, that digital teaching media was the way of the future. He and his wonderful wife Jan welcomed us (despite our junior status) warmly to their home. Aldo was a gifted leader and had an insatiable drive to benefit his patients and improve the care of all pregnant women around the globe. In addition, he was a remarkably humble man and as such he is among the great leaders of our profession.

We understand that, in his honour, a symposium will be held at the RCOG, in the UK, and we hope that our College does the same in memory of a great doctor, colleague, leader and innovator.

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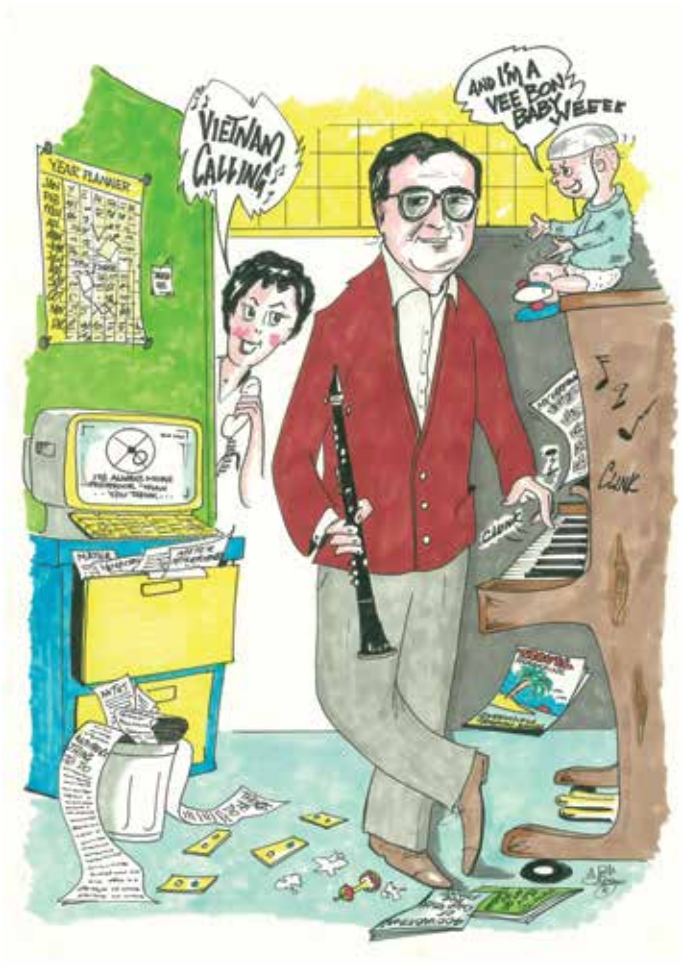
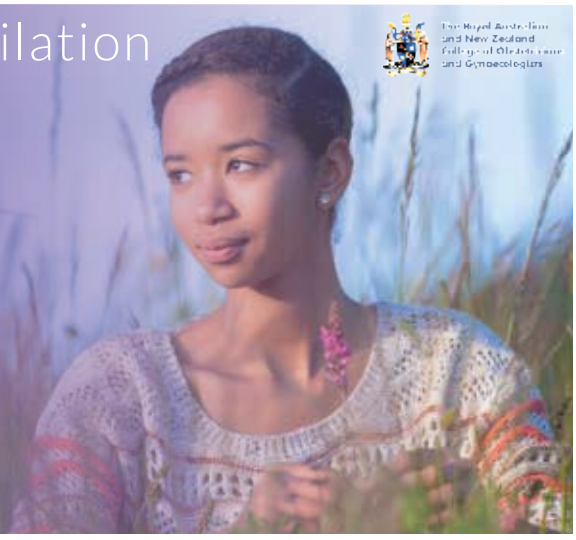
Dr Eva Kretowicz
MBBS, FRANZCOG

Dr Julie Lindstrom
MBBS, FRANZCOG



The cartoon of Dr Aldo Vacca that his registrars presented to him. Image reproduced and used with permission.



Aldo Vacca's legacy

I approached with interest the comment by Prof Dietz on the legacy of Aldo Vacca (*O&G Magazine* Vol 17 No 1 Autumn 2015 p55). Unlike Prof Dietz, there were many of us who were privileged to be trained by Aldo. He was an example to a huge number of trainees coming under his watchful eye, in particular with his keenness to supervise (with a dose of Mediterranean 'cajoling' along the way). None of us could forget his daily ward-round of the neonatal cots, focusing on the vacuum-assisted babies of the previous day. Woe betide any registrar who was associated with a chignon away from the flexion point, or worse still a 'failed vacuum' with successful forceps. We must all remember being gently taken to the nursery to inspect said fetal skull and to account for our actions. I remember to this day the immortal Vacca screensaver 'It's always more posterior than you think', the 'getting to know you pull', those cardigans, the attempt at a 'VeeBon' and his genuine joy at being presented with a fabulous caricature on his retirement from the Mater Hospital.

Sadly, by the end of the first paragraph, it is clear why this one-pager has been written, as soon as Prof Dietz states: 'It is a pity Australians don't realise how big a difference Aldo's work has made for women in Australia, and it's even worse that his great work is slowly being undone, now that his championship is lost to us.' We all have our own perspectives, held with varying degrees of veracity, tenacity and passion; however, their expression needs to be respectful, appropriate and not disguised within 'sheep's clothing'. It's supposed to be about Aldo, a great educator, obstetrician and contributor to international management of birth, not about that which Prof Dietz believes (unilaterally and vociferously) is 'our irrational obsession with caesarean section rates'.

O&G Magazine could have done so much better.

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Dr Aldo Vacca is presented with the RANZCOG Distinguished Service Medal, by the then President Dr Rupert Sherwood and Dr Gino Pecoraro, then Board member, in the Frank Forster Library in March, 2011.

Author's response

In his letter to the editor, Prof Welsh takes exception to me using the words 'irrational obsession with caesarean section rates', and I agree the statement requires elaboration.

There is a great need to debate this topic, which is affecting not just personal relationships and institutions, but our entire profession. Prof Alec Welsh is quite aware of this, given that he is working at the Royal Hospital for Women in Randwick, an institution where this 'irrational obsession' was likely the main factor responsible for a tripling of transfusion rates a few years back.[1] Excessive second stages of labour, denial of elective caesarean on maternal request, an emphasis on increasingly risky VBAC and increasing reliance on forceps rather than vacuum are all results of this obsession. I've recently summarised the effect of the latter in a review.[2]

Aldo Vacca's legacy is the prevention of tens of thousands of cases of major maternal trauma, and his legacy is in danger of being undone. That is blatantly obvious, even if this inconvenient truth conflicts with Prof Welsh's opinions.

If it took any single issue to convince us that *O&G Magazine* fulfils an important role, this controversy would surely suffice.

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After the storm

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Tropical Cyclone Pam struck Vanuatu in March 2015. With winds over 250kph, the category-5 cyclone ravaged the island country, causing deaths, casualties and massive destruction. Months later, the work to rebuild is on going.

Cyclone Pam has affected more than half the total population of Vanuatu, with 160 000 people losing homes and belongings. More than 80 per cent of houses in many islands and communities were flattened, resulting in widespread homelessness. In the immediate aftermath, the displaced thousands took refuge in evacuation centres, in island caves or in the neighbouring homes that had survived the force of the cyclone. In the capital Port Vila alone, more than 3000 people were displaced from their homes. Of course, it is not just their homes these people have lost; they have also lost all their belongings, their gardens and their livestock.

Cyclone Pam caused extensive, severe damage throughout the country; it severely affected four of the six provinces in Vanuatu.

The impact on the health system has been huge, causing severe disruption of essential health services, largely owing to damaged buildings, a lack of medicines and supplies, staffing shortages, the disruption of water and energy supplies, and interruption of telecommunications, road and sea transportation.

On 13 March, the government declared a state of emergency, activated all emergency operation centres in the country and called for international aid. People urgently needed basic necessities – food, water, shelter and life-saving emergency healthcare services. The international aid community was quick to respond with assistance to prevent further mortality and morbidity. The first foreign medical staff arrived within two days of the cyclone. A total

Half the population of Vanuatu has been affected by the damage caused by Tropical Cyclone Pam.

With many health facilities damaged, pregnant women are less likely to receive antenatal care.

of 20 medical teams offered assistance to Vanuatu. Most of them arrived in the first two weeks from Australia, New Zealand, France, Japan, Fiji, the Solomon Islands, New Caledonia, the US, Germany, Philippines and Israel, and worked tirelessly in difficult situations to save lives and support the health system. The teams consisted of 166 medical professionals: 54 doctors, 40 nurses, 24 paramedics, 12 midwives, six pharmacists and 35 support staff.

More than 160 000 people, living on 22 islands, have been affected. The most severely affected island of Tanna had the highest number of emergency medical evacuations: more than 30 out of a total of 72; 25 of whom were children under five. The main referral centre, Vila Central Hospital, had to cope with increased emergency clinical loads and a demand for better health services. A woman was reported to have delivered a baby by herself on the island of Paama in the middle of strong winds and rain during pitch-dark hours of the night. Many similar stories of frightening experiences scar the memories of those affected.

Post-cyclone recovery – health response

With international humanitarian aid and support, a government-led, multi-cluster assessment has been staged to identify on-going humanitarian priorities, gaps in life-saving assistance and early recovery needs. As the country transitions from a state of emergency phase to a recovery phase, the areas of greatest health concern include the following:

- To date, six out of the 71 health facilities assessed were completely destroyed by Cyclone Pam and a further nine sustained major damage. A return to continuity of essential health services in both hospitals and primary-care facilities is still some way off.
- Health staff whose homes were damaged are slowly returning to work post-cyclone.
- There is poor access to essential health services, especially for mothers, infants and children. More women may forego antenatal care and disregard the importance of attending a health facility for the birth or giving birth with a skilled birth attendant present.
- Continuity of patient care: patients on long-term treatment have run out of medications and find it difficult to replenish supplies, owing to transportation difficulties.
- Water and sanitation systems have been damaged and basic hygiene is a huge challenge.
- Disease outbreaks are likely to occur, especially of communicable diseases: skin infections, respiratory illness, diarrhoeal diseases, leptospirosis and vector-borne diseases.
- Food security and shortages: 96 per cent of crops have been destroyed and people are reliant on food aid. Current

Even with food distribution targeted at pregnant and lactating women, and children under five, it is difficult to access fresh fruit and vegetables.

food distribution to about 110 000 people will end in June. Foodstuffs have been limited to rice, noodles, tinned meat and fish. Fresh fruits and vegetables will be a rare commodity on the islands in the next six months. Adequate nutrition is targeted at pregnant and lactating women, and children under five.

- Large numbers of livestock have died, affecting adequate supplies of local meat for export and consumption.
- Severe wasting and malnutrition are likely to increase, owing to compromised food supplies and health services. The destruction of food crops has significant implications for nutrition until food stocks are restored.

Opportunities for recovery

Cyclone Pam has had a serious development impact on Vanuatu, affecting its long-term national economic plan and social services, particularly education and health. It will take years of rebuilding and restoration to return to pre-cyclone socioeconomic status. Education and health services have been severely affected and the health system, which was already fragile, has been further weakened. The priority needs for continuing health services include the following: support for health infrastructure and basic clinical needs; restoration of essential health services at all levels of health service delivery; staff recovery and redistribution; medicines and supplies; and overall maintenance of health facility functions. It is also important to note that healthcare staff need psychosocial support to help them cope with the demands of work and to manage their families and homes.

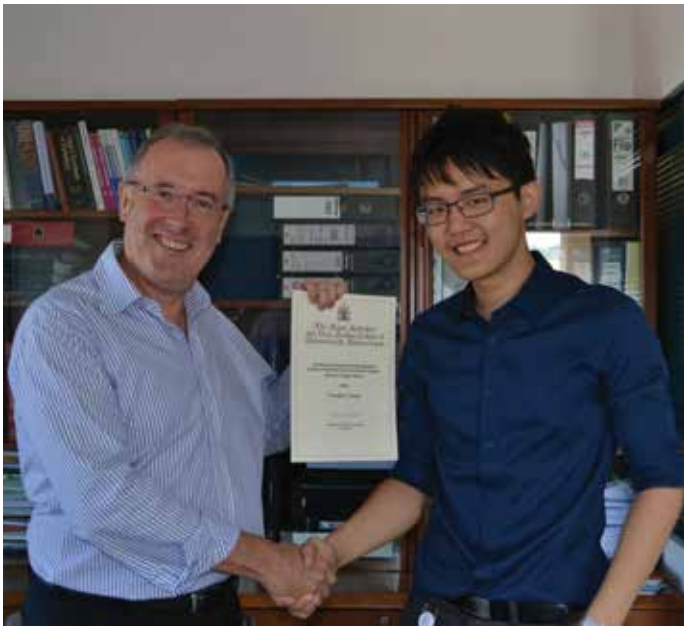
While the government has received varying types of support in response to the storm, the challenge is to sustain ongoing national development so that recovery plans continue to make progress. External assistance providers must consult with government to adequately prioritise needs. Incoming technical advisors must ensure transfer of knowledge and skills that build and strengthen local capacity to restore stability and help to build a stronger health system.

How to help

RANZCOG and Send Hope Not Flowers have joined together to support reproductive health colleagues in Vanuatu with practical assistance to help speed the resumption of O and G and reproductive health services. Donations to assist Vanuatu are welcome at the Send Hope Not Flowers website (www.sendhope.org). A receipt from Send Hope Not Flowers will be issued for all donations. Please contact Carmel Walker, Senior Co-ordinator Asia Pacific & Global Women's Health, for further information: cwalker@ranzcog.edu.au .

RANZCOG Women's Health Award winners for 2014

Sarah Wood, pictured at her graduation ball, is presented with the RANZCOG Women's Health Award for 2014.



Reyben Tang, from the University of New South Wales, is presented with the RANZCOG Women's Health Award for 2014 by Prof William Ledger, Head of School.

Marking ten successful years, the Royal Australian and New Zealand College of Obstetricians and Gynaecologists is proud to present the RANZCOG Women's Health Award 2014 to the following outstanding university students in obstetrics and gynaecology from medical schools across Australia, New Zealand and Papua New Guinea.

- Stephanie Built, University of Auckland;
- Sarah Wood, ANU Medical School;
- Yostina Tadros, Bond University;
- Timothy Everett, Flinders University;
- Andrea Coleman, Griffith University;
- Usama Shahid, James Cook University;
- Jia Hui Lee, Monash University;
- Alison Elizabeth Munro Jones, University of Newcastle;
- Reyben Tang, University of New South Wales;
- Kayla Mackinnon, University of Notre Dame (Western Australia);
- Samantha Ennis, University of Notre Dame (Sydney);
- Alice Hickey, University of Otago;
- Tracey Jeff and Paul Mondia, University of Papua New Guinea;
- Constance Leung, University of Sydney; and
- Portia Smallbone, University of Western Australia.

Committed to promoting the specialty of obstetrics and gynaecology as an exciting and valuable career option, the College envisages this award will help foster awareness of the specialty among high-performing medical students.

Notice of Deceased Fellows

The College was saddened to learn of the death of the following Fellows:

Dr Richard Francis Drake, Qld, on 30 January 2015
Dr Ralph William Forman, NSW, on 16 April 2015
Dr Laurie Thomas Williams, Vic, on 22 April 2015