



Australian Medical Student Journal

The future of personalised cancer therapy

Guest

Global inequities and the international health scene

Review

Immunisation and informed decision making

Feature

Off-label prescribing: Legal & ethical concerns

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Australian Medical Student Journal

Volume 3, Issue 1 | 2012

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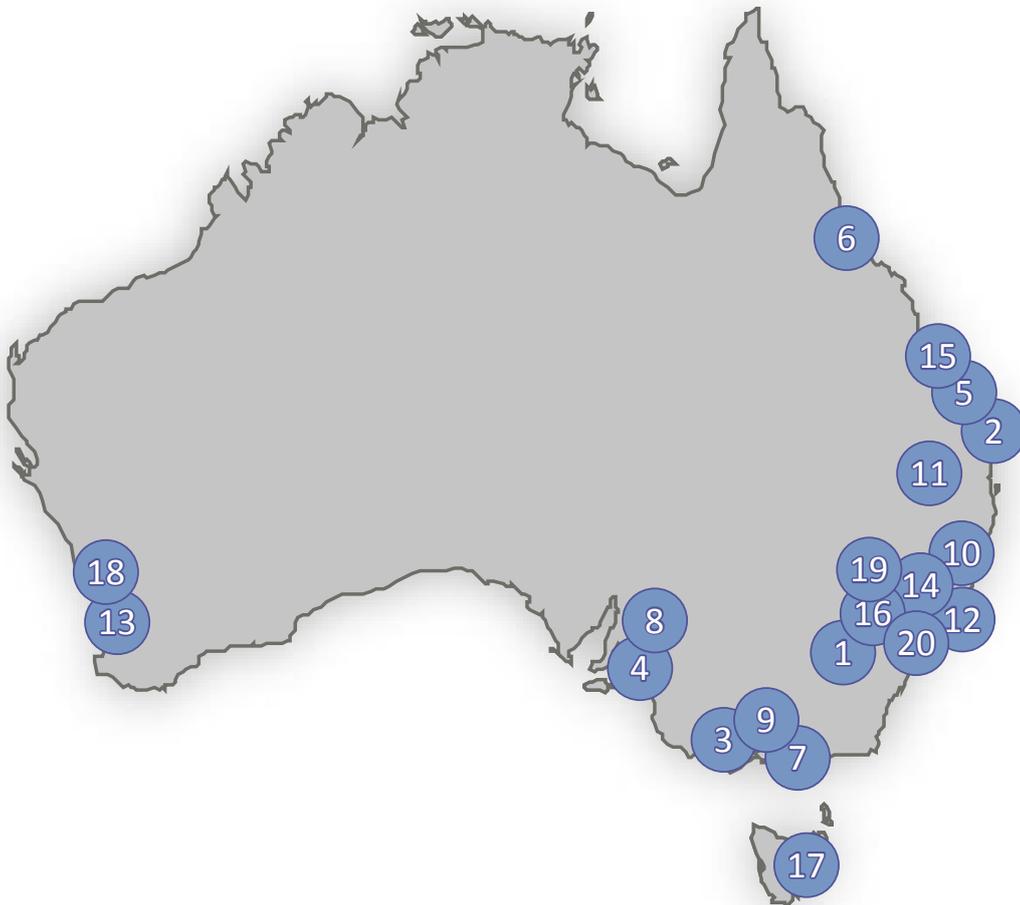
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Humble beginnings to life changing discoveries

Grace Leo

Internal Director, AMSJ

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Ania Lucewicz

Editor-in-Chief, AMSJ

Welcome to Volume 3, Issue 1 of the Australian Medical Student Journal.

As always, we hope this issue offers excellent food for thought for budding doctors and researchers.

From our deputy editor, Hasib Ahmadzai, comes an editorial reflecting on the role of medical students in medical discoveries in the past. It goes to show that when medical students get to work, it is amazing just what we can achieve!

Australian of the Year and plastic surgeon Prof Fiona Woods entertains us with stories of how her early experiences stretched her mind and informed her later discoveries. Our other guest author, Sir Gustav Nossal, uses his decades of research experience in immunology to provide an insightful discussion on the serious inequalities present in global health.

The award for best article for Volume 3, Issue 1 of the AMSJ goes to Matthew Bray and Daniel Keating for their original research on 'Immunisation and informed decision making amongst Islamic primary school parents and staff'. Their research was considered by the editorial staff to be robust in methods and offering a unique perspective on an issue that

is not often considered by practitioners in Australia.

As a young journal, we host many changes each time we go through the publication process as we strive to continually innovate and bring readers the highest quality of student research publication.

The editorial department has undertaken many of these changes. One of our aims has been to make the AMSJ a truly Australia-wide medical journal. This issue is the first for which we have recruited editorial and production staff from almost every state. Our team has welcomed seven new editors and now represents ten different Australian universities. With both rural and urban students on board, we believe that the AMSJ is well equipped to encourage research across a wide range of medical practice settings.

This is also the first time that the publication process has primarily taken place through email and teleconference, rather than face-to-face meetings. We have particularly benefited through the adaptation of cloud technology. With this change, remote collaboration has been made easier and more efficient.

While we have engaged Australia on an organisational level, this issue sees further

efforts to bring equal readership and access to the journal for all Australian students, regardless of location. This has culminated in distribution to not just every medical school in Australia, but also their 50 rural clinical schools and campuses.

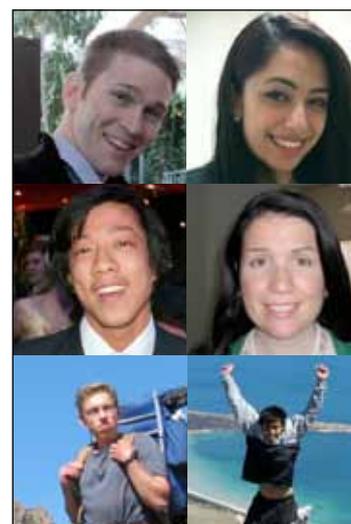
Furthermore, the AMSJ website has seen many advances to keep pace with current technology, including a touch-friendly mobile website (which can be found on your smartphone at www.amsj.org).

Other upcoming events include the next round of recruitment for the AMSJ team in August this year. We would strongly encourage enthusiastic and dedicated medical students to apply for one of the many roles available. This is a unique opportunity to become part of a growing national organisation which encourages development of critical thinking, teamwork and research publication skills.

We would like to extend our thanks to all of the voluntary AMSJ staff and external peer-reviewers for their invaluable efforts in the production of this issue. To our readers: thank you for your continued support and we hope you will share our passion for medical student research.



A few of our AMSJ staff members based in NSW at a recent meeting.
 First row (left to right): Veronica Lim, Chris Long, Alexander Murphy, Matt Schiller and Chee Kong (Patrick) Teo. Second row (left to right): Ania Lucewicz, Jenny Liu, Grace Leo, Yu Shan Ting and Aman Madan.



A few of our interstate AMSJ staff (left to right from top row):
 Michael Stuart (JCU), Tahmina Anwari (Fremantle), Ha Lu (Adelaide), Kathryn Kerr (Newcastle), Michael Thompson (Tasmania), Foong Yi Chao (Tasmania).

Ranking the league tables

Saion Chatterjee

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Fourth Year Medicine (Undergraduate)

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University league tables are becoming something of an obsession.

Their appeal is testament to the 'at a glance' approach used to convey a university's standing, either nationally or internationally. League tables attract public attention and shape the behaviour of universities and policy makers. Their demand is a product of the increasing globalisation of higher education, tighter allocation of funding, and ultimately the recruitment of foreign students. Medical schools are not immune to this phenomenon, and are banished to a rung on a ladder year after year according to a formula that aggregates subjectively chosen indicators. While governments and other stakeholders are placing growing importance on the role of league tables, it is necessary to scrutinise the flaws in their methodology and reliability in measuring the quality of medical schools.

Academic league tables, the brainchild of Bob Morse, were developed for the *US News and World Report* 30 years ago. [1] They were pioneered to meet a perceived market need for more transparent, comparative data about educational institutions. [1-3] Despite being vilified by critics, several similar ranking systems emerged in other countries in response to the introduction of, or rise in, tertiary education tuition fees. [1-3] League tables have since garnered mass appeal and now feature as a staple component of the education media cycle. They often take on the form of 'consumer guides' produced by commercial publishing firms who seek a return for their product. [1]

Although in existence for less than a decade, the Times Higher Education (THE) World University Rankings, along with the Quacquarelli (QS) World University Rankings and Shanghai Jiao Tong University Academic Ranking of World Universities are considered the behemoths of international university rankings. They provide a snapshot of the top universities overall and by discipline. From 2004 to 2009 THE, a British publication, in association with QS, published the annual THE-QS World University Rankings, however, the two companies then parted ways due to differences over methodology. The following year, QS assumed sole publication of rankings produced with the original methodology, while THE developed a novel rankings approach in partnership with Thomson Reuters. Many countries also generate national rankings by pitting their universities against each other -

Australia's answer being the *Good Universities Guide*.

League tables employ various methodologies to rank universities. Most involve a three-stage process: first, data is collected on indicators; second, the data for each indicator is scored; and third, the scores from each indicator are weighted and aggregated. [3] The THE rankings use thirteen performance indicators, grouped into five areas including teaching, research, citations, industry income and international outlook. [4] Teaching has a 30% weighting and constitutes a reputational survey (15%), PhD awards per academic (6%), undergraduates admitted per academic (4.5%), income per academic (2.25%) and PhD/Bachelor awards (2.25%). [4,5] QS also uses a similar construct to render their final rankings. In contrast, the Shanghai rankings are established solely on research credentials such as the number of Nobel- and Fields-winning alumni/faculty and highly cited researchers, and the number of non-review articles published in *Nature and Science*. [6]

The influence of ranking tables has grown to such an extent that various vested interests indulge in rankings for different reasons. [1-3,7-9] A 2006 international survey revealed that 63% of higher education leaders made strategic, organisational, managerial or academic decisions based on rankings. [7] This is not always for the benefit of students or staff, and sometimes simply reflects the desire of a senior team to appear to have had an easily-identifiable impact. It is claimed that rankings have also influenced national governments, particularly in the allocation of funding, quality assessment and efforts to create 'world class' universities. [8] Furthermore, there is limited evidence that employers use ranking lists as part of the selection of graduate recruits. [8]

Academic league tables are no strangers to criticism, reflecting methodological, pragmatic, moral and philosophical concerns. Critics argue that ranking lists have applied the metaphor of league tables from the world of sport; a simplistic and incapable tool for evaluating the complex systems of higher education. [3] Rankings are guided by 'what sells in the market' rather than the rigorous quality assurance practices of academic bodies.

The world's main ranking systems bear little resemblance to each other, owing to



the fact that they use different indicators and weightings to arrive at a measure of quality. [1-3,8,9,11] According to a study by Ioannidis *et al.*, [10] the concordance between the 2006 rankings by Shanghai and the Times is modest at best, with only 133 universities holding positions in both of the top 200 lists. The publishers of these tables impose a specific definition of quality onto the institutions being ranked, by arbitrarily establishing a set of indicators and assigning each a weight with little theoretical basis. [1-3,8] Readers are left oblivious to the fact that many other legitimate indicators could have been adopted. To the reader, the author's judgement is, in effect, final. Many academics are of the view that rankings do not take into account the important qualities of an educational institution that cannot be measured by weightings and numbers. [8]

Statistical discrepancies also compound the tenuous nature of league tables. Often institutions are ranked even when differences in the data are not statistically significant. [1-3,8] There have been many instances where data to be used in compiling ranking scores are missing or unavailable, especially in international comparisons. [1-3,8] Moreover, data availability is a source of bias, whereby publishers opt for convenient and readily-available data, at the expense of accuracy and relevancy. [1-3,8]

Another cause for concern is that rankings place a significant emphasis on research while minimising the role of education in universities. [5] Most educators would recognise that the indicators for quality

teaching and learning are limited. [1-3,8] Various proxies for teaching 'quality' are used, including average student-staff ratios. [1-3,8,11] The lack of robust data relating to teaching quality is attributed to its difficult, expensive and time-consuming nature. [2] When considering that teaching quality is one of the key dimensions of medical education, its neglected importance severely compromises the meaning of any data produced by these tables.

The main mechanism for quality assurance and evaluation amongst medical schools

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at present is regular accreditation by national or regional accreditation bodies. [5] The Australian Medical Council (AMC) is responsible for setting out the principles and standards of Australian medical education, including assessment. The 'one-size-fits-all' approach of ranking tables is a futile means to effectively measure the quality of medical schools. Medical education is characterised by a range of unique indicators, for example, clinical teaching hours and global/rural health exposure. As a direct consequence of accreditation bodies, most medical schools deliver a consistent level of education and

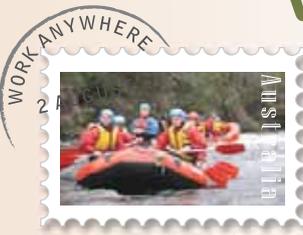
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yield competent interns to practice in the Australian healthcare system. By contrast, league tables are over-simplified assessment tools for evaluating the quality of medical education, and even have the potential to harm the standards of education. [10]

Although league tables are not exalted and revered to the same degree as in the US or Europe, Australia is inadvertently heeding this imperious trend. League tables are nothing more than 'popularity polls', and should not become an instrument for measuring the quality of universities and medical education.

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Medical students, innovation and medical discoveries

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Introduction

Some medical students sometimes regard themselves as an unimportant, unwanted and superfluous member of the medical team, lacking experience and often finding themselves standing in the way, unsure of what to do when a medical emergency arises. However, an examination of medical history reveals that medical students have been instrumental in contributing to new medical developments and discoveries. Their contributions are a reminder of how meticulous study and hard work in clinical and scientific research can lead to significant achievements on a large-scale. A few examples of significant medical student discoveries include the discovery of heparin as a major anticoagulant, identification of insulin in the control of blood glucose and diabetes management, ether anaesthesia and the discovery of the sinoatrial node. With medical schools worldwide and across Australia increasingly incorporating research programmes into medical curricula, medical students' contribution to medical innovation will hopefully continue into the future.

Famous medical student discoveries

Diabetes research

In 1869, Paul Langerhans (1847-1888) a German medical student from the University of Berlin, studying under the famous pathologist Rudolf Virchow (1821-1902), described pancreatic islets in his thesis, and was also the first to discover and describe dendritic (Langerhans) cells in the skin. [1,2] The exocrine pancreas had been significantly investigated since the 16th century and the organ was regarded as a "salivary gland". Langerhans began his research on the microscopic anatomy of the pancreas using pancreatic tissue from humans, rabbits and salamanders. He completed his work within 6 months - the length of a modern day medical school research project - identifying the presence of "irregularly polygonal" cells with clear cytoplasm diffusely scattered throughout the gland. Later, the French histopathologist Edouard Laguesse discovered that the pancreatic islets were in fact a source of internal pancreatic secretion, later determined to be insulin. [1]

Insulin was later discovered by a Canadian medical student, Charles Herbert Best (1899-1978) and a young surgeon, Frederick Grant Banting (1891-1941). As a 22-year old medical student who had just completed

his physiology exams, Best was introduced to the 28-year old medical practitioner and surgeon Banting, by his physiology professor, John JR Macleod. [2] Under Macleod's research laboratory and with difficult working conditions, Banting and Best were determined to prove their hypothesis that the factors preventing diabetes mellitus were found in the Islets of Langerhans. These cells could be isolated from a dog, after ligating the pancreatic duct, which caused the exocrine pancreas to atrophy. Banting argued that injecting an Islet extract into a diabetic dog would resolve its symptoms. [1] After much failure, they identified a purified pancreatic extract and tested it by intravenous injection into a diabetic dog. Thus, by late 1921 they were able to show insulin's efficacy in treating canine diabetes. By February 1922 they performed the first human insulin injection to successfully treat Leonard Thompson - a fourteen year-old diabetic who then lived for 13 years (but later died from a motor vehicle accident) with diabetes after initially being expected to live for a few weeks. [2-4] In 1923 Banting and Macleod were awarded with the Nobel Prize and Banting's prize money shared with Best, who was still a medical student at the time.

Anatomy

English medical students of the 18th and 19th centuries had an infamous reputation for bodysnatching from graveyards to provide a sufficient numbers of cadavers for their anatomy dissection studies. [5] The study of anatomy and acquisition of cadaveric material is now very different, but these fanatically enthusiastic early medical student pursuits also paved the way for positive discoveries in the fields of anatomy and surgery. Martin Flack (1882-1931) was an English medical student from Kent, who in 1903 started work at the London Hospital with the famous anatomist Sir Arthur Keith (1866-1955). On returning from a holiday Keith was informed by his excited medical student of a "*wonderful structure he had discovered in the right auricle of the mole.*" [6,7] This discovery of the sinoatrial node was made whilst Flack spent his summer holiday dissecting the hearts of moles, mice and frogs with the same surprising results. The structure he had identified resembled the atrioventricular node and thus they concluded that the sinoatrial node was the cardiac pacemaker - the origin of the "*dominating rhythm of the heart.*" [8]

The pancreaticobiliary sphincter was also

a famous discovery made by a 23-year old Italian medical student from the University of Perugia, Ruggero Oddi (1864-1913). Oddi studied the actions of the sphincter and observed that it controlled the flow of bile from the liver into the duodenum. He was also credited with suggesting that sphincter dysfunction was implicated in biliary tract disease. [1] Other influential student discoveries include William Harvey's observations at the University of Padua that venous valves provided unidirectional blood flow, and the discovery through chick embryos that the heart had an important role in pumping blood via the systemic circulation. [9] Spermatozoa were also similarly discovered by the medical student Johan Hahm (1651-1723) in 1671 after he provided a sample of urethral discharge from a patient with gonorrhoea to the Dutch lensmaker and "father of microscopy" Antoni Van Leeuwenhoek in which he had identified small living "animalcules". [1] Leuwenhoek then studied his own semen, identifying the presence of motile animalcules, with blunt round bodies and thin, undulating transparent tails, which he then proposed was involved in fertilising the ovum. [1]

Anticoagulants

Heparin is a major anticoagulant used in modern day medical and surgical practice to prevent and treat thromboembolism. This major pharmacological agent was discovered by a second-year medical student from Johns Hopkins University, Baltimore, Jay McLean (1890-1957). McLean worked in a coagulation laboratory under the guidance of the physiologist William Henry Howell, where he was aiming to investigate procoagulants. In 1961 he isolated a fat-soluble phosphatide anticoagulant in canine liver tissue. [1,10] McLean unfortunately did not further pursue this investigation as he was more interested in procoagulants and he moved to Pennsylvania, so Howell continued research on this anticoagulant. This would later be termed heparin (from Greek, hepar for liver) and by 1937 trials of heparin use had commenced, after which heparin was considered a safe and effective anticoagulant. Unfortunately, however, the discovery of heparin was to become a major area of dispute and a posthumous attempt for a Nobel Prize for McLean later failed. [1]

Ether anaesthesia

While it is argued that the first use of ether anaesthesia for general surgery was by

Table 1. List of Australian medical schools including those which offer a research component as part of the course. Information gathered from university websites and course guides. Information is current as of 14th March 2012.

Name of Medical School	Research component included within the degree	Degree duration (years)	Higher research degrees in conjunction with medical degree
Australian National University	Compulsory 1.5 year research project during semester 2 year 1 to end of year 2 in conjunction with other medical studies.	4	
Bond University	One 8 week research placement available during 5th year only for selected students. No other formal research projects.	5	
Deakin University	No formal extended research projects offered with medical studies.	4	
Flinders University	A one year BSc (Hons) project is available to selected students for research.	4	
Griffith University	No formal extended research projects offered with medical studies.	4	
James Cook University	Option for medical students to undertake two years of research in parallel with year 5 and 6 with the award of MBBS (Hons), or to undertake an additional year between years 3-4 or years 4-5 as a full time BMedSci Honours research project.	6	
Monash University	No research as part of medical degree, but option to undertake one additional research year with a BMedSc (Hons) project prior to starting clinical attachments.	5	
University of Adelaide	All students are required to complete a research proposal project in year 4. There is also an option to undertake a one year B.Med.Sc (Hons) project for further research.	6	
University of Melbourne	One semester of research in year 3 and in year 4 as the "Scholarly Selective" courses, with compulsory annual student conferences in years 1-4.	4	Medical course was converted to an MD degree in 2011, with an increased research focus.
University of Newcastle	No formal extended research projects available, but there is option of undertaking an additional BMedSci Honours year of research at least after completing 3rd year of BMed.	5	
University of New England	No formal extended research projects available, but there is option of undertaking an additional BMedSci Honours year of research at least after completing 3rd year of medical studies.	5	
University of New South Wales	Compulsory one year Individual Learning Project (ILP) during years 3 or 4, or a BSc (Med) Hons year during year 4. There is also a medical lateral entry scheme after successful completion of a medical science degree, followed by a BSc (Med) Hons year prior to entry into 4th year medicine.	6	
University of Notre Dame	Honours Research Project available for selected 4th year students in conjunction with their final year.	4	
University of Queensland	A one semester Honours research project is offered during 3rd year.	4	
University of Sydney	An optional 6-12 month research project is offered as part of the MBBS (Hons) project and can be completed within the 4 year course.	4	Plans are in progress to convert the MBBS to the MD degree.
University of Tasmania	Students have an option of completing an extra Research Honours year as part of the MBBS (Honours).	5	
University of Western Australia	Compulsory one year Research and Discovery project undertaken in 4th year. A combined BMedSc degree is also offered in conjunction with MBBS for extended research. This combined degree is completed over 6 years, the research component is conducted part-time and longitudinally over 3 years.	6	From 2014 the MBBS degree will be converted to the MD degree.
University of Western Sydney	Optional one year honours stream research project is available apart from compulsory medical studies.	5	
University of Wollongong	No formal extended research projects offered with medical studies.	4	
Total offering research projects	5 with compulsory research programmes. 14 with additional optional research projects including an additional Bachelor of Medical Science Honours degree. 3 medical schools do not offer formal research projects as part of their course.		

William Crawford Williamson Long (1815-1878), the first recorded administration of ether anaesthesia for dental surgery was performed by a medical student named William E. Clarke in New York, 1842, in which Clarke was assisting a dentist to perform a painless tooth extraction. [11] Long was a young country doctor who is credited to have administered ether to a young man in 1842 for which a painless neck cyst removal was performed. [1]

Infectious diseases

Even as a first year medical student, Sir James Paget was contributing to significant discoveries. Although he is well-renowned for the eponymous conditions of Paget's disease of bone (osteitis deformans) and Paget's disease of the breast and nipple, his name was published as a first-year medical student for discovering the nematode *Trichinella spiralis* in human muscle, the cause of trichinosis. [12] Similarly, an Argentinian medical student, Alejandro Posadas discovered Coccidioidomycosis in 1892, describing a case report of an Argentinian soldier with cutaneous manifestations of the disease. Later, in 1926 a second medical student, Charles Smith inadvertently contracted the disease by inhaling the spores whilst working on the organism in the laboratory. He later developed pleuritic chest pain and purulent productive cough - which helped identify the clinical presentation of the disease and luckily he survived to tirelessly study the disease throughout his professional career. [13]

This list of historical medical student discovery is by no means exhaustive. However, it highlights the influence of medical students on medical research and innovation throughout history. Although current freedom of research may be limited by modern day bureaucracy, students still have chances to contribute to research, through increased university research opportunities.

The role of medical schools and research

The modern day medical student may question what is left for them to discover, as modern medicine becomes increasingly sub-specialised. The explosion in medical advances over the last few decades makes it daunting to even make a small contribution. A quick internet search may reveal that many ideas have been exhaustively investigated and

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Australian Medical Journal Aims

- To provide a medium for Australian medical students to publish their work and share ideas with their peers.
- To provide a suitable forum for students to make the transition between assignment-writing and producing publishable academic work.
- To inform students about medical topics and issues not typically addressed in core curricula.
- To facilitate discussion of current issues relevant to medical students.
- To allow Australian medical schools to showcase the research aspects of their programs.
- To provide a further incentive for students to produce high-quality work in their studies.
- To foster the next generation of Australian medical researchers and physician-scientists.
- To provide an avenue for students interested in a career in medical editing or publishing to pursue this interest as a student staff member.

recent discoveries are only possible in certain areas such as molecular biology. [1] However, with the availability of recent technologies, modern research methods and laboratory techniques, students still have many options available to unleash their creativity and pursue their interests through research. Additionally, mandatory and optional research components have increasingly become part of medical school training programmes, which provide numerous opportunities for students to become involved in working with world-expert researchers, academics and clinicians.

Of the nineteen Australian medical schools, five have a compulsory medical research project as part of the medical school's training program (see Table 1) and fourteen have either short optional research project placements or allow for an additional Bachelor of Medical Science Honours year in conjunction with the medical degree. The number of Australian medical schools offering research projects as part of their course highlights the significance of medical research for current graduates. The trend for incorporation of research programs in medical schools has also contributed to the recent development of a shift by some universities from the standard Australian MB BS towards Masters level MD degrees recognising research. [14] Although this would be a positive step towards increasing medical student research and innovation, it poses many new challenges and risks creating a two-tiered system with a divided medical profession. [15,16]

The AMSJ continues to promote student research by facilitating publication of medical student ideas and research findings. In addition

to assisting publication of student research, the third volume of the journal continues to strive in its aims (see above) of celebrating medical student success in other areas. [17] The AMSJ has now extended to become a truly nation-wide peer-reviewed journal, with our current student staff representing eleven Australian medical schools.

Conclusions

There are many opportunities available for Australian medical students to become involved in research with leading researchers, academics and clinicians. Medical students have the opportunity to contribute to ground-breaking cancer research, assist in drug trials, help with the identification of disease biomarkers and pathogenesis of complex diseases, or determine the efficacy of new surgical techniques, to name a few examples. Even if research degrees or projects are not offered by some universities, medical students should consider becoming involved in extra-curricular research in addition to their busy schedules to fuel their intellectual intrigue, assist in continuing medical and professional development and increase their general knowledge. This will help to continue the tradition of innovation, ultimately leading to further significant medical student discoveries. We hope that the AMSJ will provide an avenue for medical students to contribute achievement in innovation, with fresh ideas and novel findings in the years to come.

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The clinician-scientist: Uniquely poised to integrate science and medicine

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Introduction

Growing in the world of academic medicine is a new generation of doctors known as “clinician-scientists”. Trained in both science and medicine, with post-graduate research qualifications in addition to their medical degree, they serve as an essential bridge between the laboratory and clinic.

The development of sophisticated experimental approaches has created opportunities to investigate clinical questions from a basic science perspective, often at a cellular and molecular level previously impossible. With new and detailed understanding of disease mechanisms, we are rapidly accelerating the discovery of new preventative measures, diagnostic tools, and importantly, novel therapeutic approaches. In these emerging avenues there is not just a need for collaboration between scientists and clinicians, but a need for individuals who are fluent in both science and medicine – hence, the advent of clinician-scientists. The terms “translational research” or “translational medicine” are often associated with clinician-scientists, alluding to the notion that these people facilitate the two-way process of translating scientific findings into clinical applications (bench-to-bedside), and provide clinical data and specimens back to the laboratory to investigate underlying disease processes (bedside-to-bench).

From a student’s perspective however, these concepts can be confusing and finding their way through the breadth and categories of research conducted in academic institutions and hospitals may prove daunting. A discussion of the clinician-scientist niche and some of the challenges and opportunities faced may prove helpful.

Defining the clinician-scientist

Most clinicians at an academic hospital are engaged in research to some extent, but this tends to be mainly clinically-oriented, with patient care, treatment outcomes, and population health being broad areas commonly involved. Their day-to-day job is mostly defined by their clinical duties, often with some teaching responsibilities involved. Clinician-scientists, by contrast, dedicate a significant proportion of their time to research, typically spending $\geq 50\%$ protected time in order to be remain academically competitive. [1] Whilst still loosely defined, in a purist sense this is a clinician who is involved in research at an organ, tissue, cellular, or molecular level, as opposed to

focussing solely on whole patients as a clinical subject. Such research may not always have clinical findings that are directly relevant to everyday medical practice but the difference from a pure basic scientist is that the science has been approached with clinical relevance in mind. Interestingly, on the other hand, science itself has become inter-disciplinary and is recognising the importance of clinical relevance and translation with new ventures such as the Stanford University PhD in Stem Cell Biology where graduate science students interested in involvement with translational research in regenerative medicine undertake rotations shadowing clinicians in order to develop a clinical perspective to their research. [2] These developments indicate that not only are the frontiers between science and medicine becoming blurred, but that translational research is the exciting intersection where clinician-scientists, as well as scientists well-attuned to clinical practice, are uniquely poised to thrive.

The clinician-scientist niche

Clinician-scientists possess a distinctive set of skills, being trained as a clinician to apply scientific knowledge to patient care, and trained as a scientist with an enquiring mind designed to test hypotheses. Understanding the clinical relevance of observations in science and the ability to translate this back into clinical practice is truly the domain of the clinician-scientist, and uniquely so.

The pursuit of additional post-graduate research qualification such as a Masters or PhD has traditionally been the main pathway to becoming a clinician-scientist in Australia, unlike in the United States where combined MD-PhD programs have been well established in the past. However, the recent development of similar combined MBBS-PhD and MD-PhD programs in Australia is likely be instrumental in building a body of clinician-scientists that have been moulded specifically for this task. [3] Skills developed in scientific training essential for success in research include literature appraisal, manuscript and grant writing, and mastery of laboratory techniques, all of which are life-long skills honed over time, and which are rarely acquired in medical school.

It goes without saying that clinician-scientists are expected to be experts in both medicine and science. Anything subpar of clinical competence would pose a threat to patient safety and cannot be compromised. On the other hand without a solid commitment in research with the appropriate output in terms

of publications, conference attendance, and grant proposals, a career in research will not take off since a track record is something that needs to be built on constantly. Given that clinical training itself takes a good number of years before being able to practice as an independent clinician it is little wonder that many are unwilling to tackle both clinical and scientific careers at once. Again, this lends further credence to the MD-PhD path where scientific training would have already been completed by the end of the program, although this itself has its drawbacks, since the science gained can become neglected in the last clinical years and will need to be polished again upon completion. [4]

But where lie challenges also lie opportunities: for the determined few, funding statistics indicate that the rigorous training is entirely worthwhile. Clinician-scientists have been found to consistently perform better in national funding programs such as the National Institutes of Health Research Project Grants (United States) than their pure clinician (MD only) and basic science (PhD only) counterparts. [5] Although the pool of clinician-scientists in Australia is significantly smaller than that of the United States and data on funding trends are less widely discussed in literature, it is generally acknowledged that clinician-scientists also do well in obtaining NHMRC funding. This may be due partly to the fact that clinician-scientists are afforded more flexibility in labelling their projects as “basic science” or “clinical”, and therefore have access to funds for both basic science and clinical projects, whereas pure clinicians and scientists are generally limited to their own funding areas.

When describing the clinician-scientist niche, an aspect of research “translation” that is often neglected is the importance of the delivery of research-based medicine into actual practice. The classic bench-to-bedside process refers to the invention of a new drug, device, or diagnostic tool where the hope is that it will undergo clinical evaluation in a controlled setting with a specific patient cohort. But bringing a discovery into the market is simply the beginning, and to bring this to the general public a much more concerted effort is required involving collaboration between public health experts, policy makers, and clinicians amongst others. So drawn-out and complex is the process that it is well acknowledged that this area of “translational” research often fails, with many potentially important discoveries unable to

make changes to everyday medical practice. [6] However, clinician-scientists are well suited to play an active role in negotiating the many hurdles in this endeavour by facilitating communication between the various experts involved, whilst providing a first-hand inventor as well as treating clinician's perspective that is not only unique but critical in ensuring that an invention is appropriately implemented and evaluated. In the Australian context, the National Health and Medical Research Council (NHMRC) has recognised this gap in research translation and the Centres for Research Excellence and Translating Research Into Practice (TRIP) Fellowships are specific measures aimed to address this issue. [7]

Wearing two hats: double the challenges?

A commonly quoted recommended research:non-research ratio for workload is 75:25, with the majority of time devoted to research in order to succeed as a clinician-scientist. [8] In reality this is more likely to be exactly opposite the case, where a 75:25 ratio in favour of clinical work becomes the norm instead. [9] This may be particularly so in the early years after graduation when specialist training is being undertaken, despite the fact that this is also the time when a solid research foundation needs to be built in order to establish a clinician-scientist's academic presence. As pressing as clinical demands may be, it is widely recognised that a research career cannot flourish without negotiating some protected time from clinical duties with the hospital department.

The biggest challenge for clinician-scientists is therefore time management. In addition to patient care, clinical training, and teaching responsibilities, clinician-scientists are expected to undertake labwork, keep abreast of advances in both scientific and medical literature, and engage in professional development and conferences on both fronts. They must maintain manuscript preparation and grant proposals, complete administrative duties, and often lead research teams. To realistically keep up with these demands of juggling a dual career, the ability to delegate and seek cooperation from scientist and clinician colleagues is critical. The lack of a supportive environment and a suitable

mentor who can share their experiences and show the way can present an impossible struggle to the time-constrained clinician-scientist.

On the clinical front, to manage their workload clinician-scientists may tightly focus their interests to subspecialised areas to maintain an adequate caseload and expertise without stretching oneself too thin. This depends however on working in an environment where the volume and diversity of patients permits such subspecialisation, with appropriate facilitation by supervisors such as Department Heads. Unfortunately these conditions tend to be found only in major tertiary hospitals, relegating clinician-scientists to these settings.

Additionally, a research career is often less financially rewarding than clinical work particularly when private practice may need to be sacrificed in order to undertake lab work. This can pose a significant barrier particularly because the number of years required to gain appropriate training results in clinician-scientists being likely to be older than their scientist and clinician counterparts and may therefore have family commitments, and have often also accumulated student debts that need to be repaid. [10] Some solutions to this may be the Practitioner and Career Development Fellowships offered by the NHMRC aimed at clinicians involved in research, [11] as well as hospital and philanthropic organisation funding specifically for buying time out from clinical practice for research.

Opportunities for the clinician-scientist

For any researcher, securing funding is a lifeline in continuing their work and burnishing a track record, and it is here where clinician-scientists can be creative in sourcing their benefactors. Philanthropic organisations often affiliated with a disease or clinical cause, specialist training colleges like the Royal Australasian College of Surgeons, hospital based foundations, pharmaceutical companies, and fundraising from patient advocates are all important and significant funding avenues that clinician-scientists may find more accessible than pure scientists. [12] These grants often allow pilot projects to be undertaken in order to generate sufficient

amount of preliminary data to become competitive for major research funding such as from the NHMRC. Additionally, a number of these organisations offer clinician-scientist fellowships similar to the NHMRC.

Apart from funding success, it has also been found that many clinician-scientists opt to apply for and are successful in obtaining university academic positions. [12,13] Such engagement in academia provides synergy for research efforts by opening up institutional resources often more diverse than hospital settings, prospects for networking with like-minded professionals and mentors.

Additionally, the scope translational research itself is widening. An increasing number of academic hospitals are dedicating departments to translational research, with clinician-scientists often taking the lead. The need to prioritise translational research has been further underlined by the Chief-Scientist of Australia's recent speech calling for increase in research funding for this area. [14] Whilst these are positive developments, further input from clinician-scientists themselves is required to shape policy changes and design steps to increase their numbers.

Moving forward

An apt saying may be, "*Clinicians know all of the problems, but none of the solutions; scientists know all of the solutions, but none of the problems*". [15] This is where clinician-scientists represent a unique breed suited to fulfil this vacant niche, and are absolutely necessary in forging the next success stories of medicine. Despite the complexities of a dual career, the rewards and satisfaction in pursuing this path are evident and meaningful, and can lead to tangible health outcomes in patients. Although it is important to maintain a realistic notion that being a clinician-scientist is by no means an easy feat, it is equally important to take hope that the best of both worlds can be experienced. These perspectives are increasingly acknowledged in the form of progresses being made in the right direction to encourage clinician-scientists. In light of this, perhaps it is well worth noting that there may never be a better time than now to venture into, and indeed take charge in riding this next wave of medical evolution.

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Metformin and PCOS: Potential benefit to reduce miscarriage risk

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I am writing in response to the review article by Wong (AMSJ Volume 2, Issue 2). [1]

Polycystic ovary syndrome (PCOS) is associated with an increased risk of miscarriage, occurring in 30% of pregnancies. [2] Although the mechanism is unclear, several interrelated factors appear to increase the risk of spontaneous miscarriages, including higher luteinising hormone levels, obesity, hyperandrogenisation, insulin resistance and infertility treatments. [3]

The advantage of clomiphene citrate over metformin for induction of ovulation has been well published. However, successful achievement of pregnancy that results in miscarriage is perhaps more devastating to a patient than anovulation. The role of metformin is not restricted to its effects on infertility and ovulation alone and the potential for treatment of PCOS-related miscarriage should be acknowledged.

As medical students, we are taught to cherish randomised controlled trials and meta-analyses for their ability to eliminate potential retrospective and investigator bias. Meta-analyses [3,4] have examined the effect of metformin on miscarriage rates in PCOS patients, one as a primary outcome. [3] Both failed to demonstrate a statistically significant benefit of metformin administration on miscarriage rates. The statistical heterogeneity among the trials and authors' recommendations, that further well-designed randomised trials were required, were of concern.

The seventeen trials included in the Palomba meta-analysis [3] were scrutinised. None of the trials examined miscarriage rates as a primary outcome. Nor were they sufficiently powered to detect differences in miscarriage incidence. Metformin administration in all trials was either ceased at human chorionic

gonadotropin injection or diagnosis of pregnancy. Thus meta-analyses published to date can only indicate that there is unlikely to be a reduction of miscarriage rates in PCOS patients, when metformin is administered prior to conception and ceased in early pregnancy.

This is essentially consistent with preliminary evidence which suggests, continued use for the full first trimester or throughout pregnancy [5] may reduce miscarriage risk compared with earlier cessation. To our knowledge, only non-randomised studies have evaluated the effect of metformin use during pregnancy on outcomes in PCOS patients.

A pilot study suggested continuing metformin throughout pregnancy reduced first-trimester spontaneous miscarriage without teratogenicity. [6] These findings have since been repeated in other studies, with significant reductions in first-trimester spontaneous miscarriage rates. [7]

Although these results are promising, these studies were non-randomised, often retrospective and used historical miscarriage rates, contributing to potential bias. Further large, well designed randomised controlled trials examining miscarriage rate as a primary outcome in women who continue to take metformin in the first trimester are indicated.

Recurrent miscarriage with three or more consecutive early pregnancy losses affects about one percent of the population, but the prevalence of PCOS is 40% in this population; almost eight-fold higher than in the general population. [4] However, PCOS was only given a brief mention in the updated European Society of Human Reproduction and Embryology protocol for investigation and management of recurrent miscarriage and there was no mention of metformin as a

possible treatment. [8]

Since this updated protocol, a case study of a PCOS patient with recurrent miscarriage demonstrated live birth after physiologic pregnancy with metformin administration before and throughout pregnancy. [9] This indicates a possible role for metformin in the setting of PCOS patients with recurrent miscarriage and supports a need for further investigation.

As for the safety of metformin administration during pregnancy, the Australian risk categorisation places metformin as a category C medication, indicating no evidence for any teratogenesis or adverse foetal effects, but lacks evidence to prove this definitively. Australian and long-term overseas research of metformin use in pregnant patients with diabetes mellitus or gestational diabetes mellitus demonstrates no evidence of teratogenesis. [10]

Of the studies with metformin administration during pregnancy in PCOS patients, there have been no reports of teratogenic effect. [6,7] Meta-analysis on limited data suggested no evidence of increased risk of major malformations when metformin is administered during the first trimester. [11]

In conclusion, metformin could still be an effective treatment of PCOS in the setting of miscarriage and recurrent miscarriage. Further large, well designed randomised controlled trials examining miscarriage rates in PCOS patients as a primary outcome are indicated. Metformin should be administered throughout the first trimester in these trials, consistent with promising preliminary evidence. Patients receiving metformin during pregnancy should be counselled of the risks, but can largely be reassured from the current safety evidence.

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The cardiac surgeon, a dying breed?

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The innovation of the cardiopulmonary bypass machine in 1951 had now allowed surgeons the ability to operate on the heart without any time constraints.

It was not soon after that Russian Cardiac Surgeon, Dr. Vasillii Kolesov, had performed the first successful coronary artery bypass surgery. His success and the innovation of the heart valve prostheses had led to the rapid development of one of the most glamorous specialities of medicine. Despite this dramatic rise of cardiac surgery there has only been modest technological advances within the field. Although noticeable improvements from the standard operation including arterial grafting, off-pump surgery, small incision surgery and endoscopic conduit harvesting have been made, the reluctance to tamper with original success has meant that only a niche group of surgeons have adopted such modifications. Outside the surgical realm, advances in the anatomic treatment of cardiovascular disease has been dramatic and paramount. Percutaneous transluminal coronary angioplasty (PTCA) has since progressed from primitive ineffective use of balloon angioplasty. New drug eluting stents and strong platelet inhibitors are available for the treatment of cardiovascular disease.

Coronary vascular disease is not the only cardiac entity that is amenable to catheter-based intervention. Indeed the treatment of valvular heart disease has now been attempted percutaneously with successful percutaneous aortic valve implants in patients with significant co-morbidities, unsuitable for surgical intervention, and balloon valvotomy in mitral valve stenosis. [1] Research however is evident that such percutaneous interventions (PCI) are by far inferior to the corresponding surgical approaches. Currently, percutaneous valvular interventions utilise first generation devices and one can be certain that newer devices that are more deliverable, user friendly, efficacious and safer will be available in the near future. Not too dissimilar to exponential growth of PTCA, the impact of percutaneous valvular interventions will soon be apparent. This is undeniably having numerous implications on the future of cardiac surgery. With an aging population and a preference for minimally invasive therapeutic intervention what does the future hold for cardiac surgery? In a study published by the Australian Institute of Health and Welfare, the number of PTCA operations has dramatically increased between 2000–2001 and 2007–2008 with

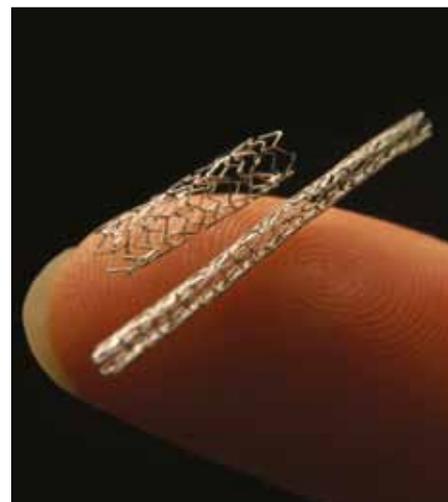
Saissan has a key interest in cardiovascular surgery and medicine. The writing of this article stemmed from his own personal interest into the future of cardiac surgery amidst the growth of percutaneous interventions.

the number of PCIs performed increasing by 57%. [2] Subsequently there has been a 19% reduction in the number of coronary artery bypass grafts performed between 2000–2001 and 2007–2008, from 16,696 to 13,612. [2]

Extrapolation of the above data shows clearly that there will be a reduction in the number of operations performed through median sternotomy. However this route is not obsolete, nor will it be so in the near future. Despite the advances in PTCA, the surgical approach is still required for those with multivessel disease and diabetic vessel disease. Coronary bypass grafting has been an effective strategy in these patients and will continue to be effective.

Treating ischaemic heart disease, has led to another problem of congestive heart failure which is on the rise with 30,000 plus new cases per year in Australia alone. [3] A large percentage of these patients have functional mitral valve regurgitation and are refractory to medical therapy requiring surgical intervention. A limited heart donor pool for transplantation has resulted in heart failure patients requiring other surgical treatments including the use of annuloplasty rings, the Dor procedure, direct remodelling, left ventricular assist and total artificial heart devices. All of which are significant advances in the area of heart failure surgery, improving patient mortality and morbidity. The surgical treatment of atrial fibrillation is another frontier that is in its infancy. The Maze procedure has been associated with conversion rates of up to 99%. This is far superior to the 50% of patients that will sustain a sinus rhythm with percutaneous catheter ablation or medical therapy. [4]

Those within the cardiac field state that there will be a shortage in qualified cardiac surgeons being able to combat high risk cases in the future due to inadequate training consequential of catheter-based intervention. Training programs already have a difficult time providing effective clinical training in many open procedures including valve repair, complex bypass grafts, off-pump surgery and homograft valve surgery. Technological advances will result in a further subspecialisation of the field and move away from the “general” cardiac surgeon. Small volume cardiac surgery hospitals will diminish with the future progressing towards a limited number of superspecialised cardiothoracic surgical institutions centred in metropolitan



areas that are able to combat the high risk difficult cardiac cases.

Currently, at the Australian college of surgeon level, there is a push towards a combined vascular and cardiothoracic training program with cardiothoracic fellows already pursuing fellowships in vascular surgery and vice versa as the differing surgical skills required in the two fields will complement each other, better equipping the surgeon with skills to utilise modern technological devices and resulting in an amalgamation of both specialties. Countries outside of Australia, such as Germany, Canada and Japan have always had separate paths for training in Cardiovascular and Thoracic surgery. Perhaps one may see a shift towards these countries in the future.

For those who believe the cardiac surgeon is a dying breed, this is far from the truth and a mere myth. Interventional cardiologists have become more skilled and adventurous with the catheter-based technologies, but they are limited to that one approach. Cardiac surgery will expand as it encompasses newer technologies. The next generation cardiac surgeons will be equipped at complex bypass grafting, heart transplant and congestive heart failure treatment modalities, percutaneous mitral valvular repair and be equipped with endoluminal vascular surgical skills. A change from an individual treatment approach is also required in the field of cardiac medicine, with a multidisciplinary team comprising of both the cardiac surgeon and the cardiologist. At the end of the day, it is the patient's interest that should be the centre of focus, eliminating conflicts between areas of expertise and allowing the practice of evidence-based medicine.

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Immunisation and informed decision-making amongst Islamic primary school parents and staff

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Background: The Islamic community represents a recognisable and growing minority group in the broader Australian context. Some sectors of the international Muslim community have voiced concerns about the ritual cleanliness of vaccines, and seen subsequent lower levels of compliance. Anecdotal evidence suggests Australian Muslims may hold similar concerns. **Aim:** This study aims to evaluate the information and knowledge with which Islamic parents and staff are equipped to make decisions about immunisation. **Methods:** Parents and staff at an Islamic primary school were recruited through survey forms sent home for voluntary completion. These surveys were designed to assess the sources of information and level of confidence regarding immunisations as well as highlighting personal perspectives of the participants and misapprehensions. All participants identified as Muslim parents. **Results:** 40.7% (n = 64) of respondents were not confident that they knew enough about vaccines to make good decisions, while 73.3% (n=115) respondents stated a personal desire for further education about vaccinations and vaccination schedules, suggesting a significant degree of uncertainty associated with the amount of information currently accessible to this cohort of the community. Qualitative responses reflected concerns associated with side effects and the halal nature of vaccines. As these responses included a perceived information gap about material risks, it raises the possibility of invalid consent. Parents obtain information from a variety of sources, the most popular being their general practitioner. However, our data suggested that the public health nurses of the shire council facilitated better knowledge outcomes than general practitioners. **Conclusion:** By taking the time to communicate material risks to Muslim parents, health professionals ensure confident, informed decision-making and consent.



British Muslims not to vaccinate their children against diseases such as measles, mumps and rubella because they contain substances making them unlawful for Muslims to take."

Concerns have been raised in the broader medical fraternity in relation to how statements such as this have influenced Islamic patient's compliance with immunisation, with data demonstrating a decrease in immunisation rates in majority Muslim countries such as Nigeria [4] and Pakistan [5], where leaders and clerics have made complex claims against the safety of vaccines. The level of non-compliance that resulted from these attitudes has set back efforts to eradicate polio worldwide. [6] In response, Warraich [7] made calls for further study into Muslim populations' attitudes towards vaccination. In the Australian context, Zwar [8] mentions that there is "anecdotal evidence that Australian Muslims may share the concerns and fears about vaccination safety" held by their brethren overseas.

Having identified the need for more data from the Muslim Australian perspective on vaccines, we endeavoured to assess the information sources and knowledge of the members of one diverse Islamic community, a primary school. Focussing on the degree to which parents are capable and confident to make informed consensual decisions about their child's immunisations, we endeavoured to determine the extent to which the data reflects trends of unease, and to provide some insight into what gives rise to such concerns.

Methods

This project received ethics approval from the Community Based Placement Program conveners, mandated by the Monash University Human Research Ethics Committee (MUHREC) to approve low impact research.

A mixed methods design was employed. A survey, designed by the authors, was used to collect qualitative and quantitative data anonymously from participants, who were parents of the students who attended the Australian International Academy King Khalid Campus primary school, and members of staff who were parents (irrespective of where their children attended school). Conducted as part of a community based health promotion project, the school agreed to host the researchers and provide supervision on the condition that sensitive

Introduction

The Islamic community presents a recognisable and growing minority group in the broader Australian context. In light of the nature of their religious fidelity, Islamic patients will bring different attitudes and knowledge to the clinical setting, requiring sensitive and appropriate medical attention. [1] A working knowledge of the core tenets of Islam allows clinicians to provide culturally relevant information to facilitate informed consent and decision-making. For example, the prohibition in Islam against receiving pork and other unclean meat products ("haram"), and the inclusion of derivatives from these in some surgical and pharmacological interventions can be an important consideration to convey, and potentially damaging omission to make in a consultation. [2]

While there is a corpus of published information pertaining to Muslim cultural considerations in medical and especially nursing practice in Australia, we identified a gap in the literature in relation to attitudes and behaviours towards immunisation. Some isolated voices in the large religious grouping of Islam have voiced major concerns about haram or unclean content in vaccines: Dr Abdul Majid Katme [3], of the 'Islamic Medical Association of Britain' is reported as "urging

questions pertaining to demographics or religious sensitivities were not explicitly asked.

Participants were recruited through one of two methods: the first being hand delivery of surveys to staff with children of their own (thereby parents themselves), and the second through the bi-monthly newsletter received by every family within the school community. Surveys were accompanied by corresponding consent documents and explanatory statements. Consent forms were received before inclusion of data. A total of 300 surveys were distributed to potential participants.

Key measures of interest were the information sources and knowledge with which these parents are equipped to make decisions surrounding vaccinations for their children and themselves. Thirteen survey questions were organised into three domains: "Obtaining Information" asking about where their knowledge about vaccines was sourced, "Concerns" which assessed for misapprehensions and misinformation about vaccines, and "Vaccines" which invited them to indicate how confident they felt in the process and their level of understanding, and their desire for more education on vaccines. At the end of those questions a single space was given where respondents could write any comments or questions sparked by the survey. Additionally, individuals surveyed were asked to include the year level of their eldest child in order to allow comparison of data across a spectrum of child age as an indicator of length of parent exposure to the immunisation process. No other demographic data was collected at the request of the school.

Descriptive statistics were used to analyse responses, with bivariate analysis of statistics to assess correlations between sources of information, age of eldest child and degree of confidence and knowledge about vaccinations. The narrative provided as feedback was also analysed for themes.

Data were analysed using Microsoft® Excel 2003. Qualitative responses were examined for recurring themes and considered in conjunction with statistical evidence as a means of determining study results.

Results

The researchers received a total of 157 validly completed survey forms out of the 300 distributed to the parents and staff of the school, a 52.3% response rate. No differentiation was made between parent or staff member status within the school as all participants were Muslim parents. In accordance with state legislation, all children of respondents were fully immunised at the time of enrolment. 15 respondents chose to use the space provided in the survey to give qualitative feedback, comments from which are interspersed below into the relevant domains.

Obtaining information

Participants of the study indicated that knowledge and guidance regarding immunisation were gained through a multitude of sources. The research confirmed that all participants had undertaken information seeking regarding childhood vaccination.

Surveys illustrated that 80.9% (127/157) of participants had used more than one source to assist in the decision-making process; while only 19.1% (30/157) had relied solely upon a single source. Of the 30 who had based their perspectives upon one source of information, 90.0% (27 out of 30) had consulted a healthcare professional - general practitioner (GP) or nurse, while the remaining 10% (3 out of 30) all received input from the local council. Flyers, (3.2%), friends (20.4%), internet (22.9%) and media (26.1%) were all used, in conjunction with other resources, to aid in the enhancement of their vaccination knowledge. Results indicated that 86.0% of all participants had sought education from GPs making them the most commonly accessed source. *"I go with what my local doctor tells me to do, which I assume was the best thing to follow,"* was the feedback received from one participant.

Concerns

One respondent commented: *"I don't believe enough information*

is provided to families about each vaccination, what it does and the side effects." When asked about possible health concerns associated with vaccinations, 50.0% of all respondents (78 out of 157) were not aware of the possible side effects of vaccinations. In fact, 75.8% (119 of 157) of participants stated that they were concerned that vaccinations would have adverse outcomes on their children's health.

Vaccines

"I wish there was more information about it as we took it as it is a must and the government encourages it," remarked one respondent. Only 60.3% (93 of 157) of parents were sufficiently comfortable with their level of knowledge to make an informed decision pertaining to their child's immunisations. This suggested that almost 40.0% (64 parents and staff) were not confident in their ability to make an informed decision for themselves or their family. Furthermore, 73.3% (115 of 157) stated a personal desire for more information about vaccinations and vaccination schedules.

When comparing knowledge confidence between those who received information from a GP versus those who received their information from the shire, council nurses, the latter group had slightly better outcomes than GPs (73.5% to 71.1%). The value of increased engagement with council nurses was highlighted in our report recommendations.

The constituents of vaccines were also highlighted as a concern in the qualitative responses: *"I wanted to know what the vaccines were made of."* In particular, the halal status of vaccines was brought up in this comment and others: *"Hopefully you could work on making a vaccine that will be significant with our religion background which is Halal Vaccine (without pork products)."*

Discussion

This research represents a sizable study into the Australian Muslim community's approach to immunisation: the largest published study involved only 22 informants belonging to one ethnic group. [9] We valued the opportunity to undertake our fieldwork in a school environment, because it provided a snapshot of the broad cross-section of individuals who make up this community, and the attitudes and knowledge of those who make decisions on vaccinations. In the future, it would be useful to explore how patient-centred factors, such as education and language impact on decision-making.

Education and side effects

The emergent theme was that the greatest concerns could be traced back to accessing relevant information about vaccination, with 73.3% of respondents having stated a personal desire for further education about vaccinations and vaccination schedules. This suggests some dissatisfaction with respect to their own levels of knowledge around vaccines and the education provided about vaccines as part of their decision-making. As a result of this disparity our research saw a startlingly high proportion of respondents (75.8%) concede concerns that vaccinations would have adverse outcomes on their children's health. Half of all respondents also admitted ignorance with regards to potential vaccine side effects in the survey.

Side effects are not uncommon with vaccines, and a sure cause for concern amongst parents. The degree to which the study findings illuminated participant's limited existing knowledge pertaining to side effects involved with vaccination, both qualitatively and quantitatively, indicates a dereliction of duty on the behalf of the general practitioners administering vaccines. This is an example of a process-centred barrier to informed consent. [10]

One of the consequences of this lack of knowledge by decision-makers is evidenced by the 40.76% of respondents who did not feel well equipped to make good decisions for their families. This reflected in comments such as this from one respondent: *"I go with what my local doctor tells me to do, which I assume was the best thing to follow,"* sentiments echoed across the world. [11] We propose that this lack of confidence, combined with a suggested sense of a culture of

paternalism, remains prevalent in the doctor-patient interaction with regards to vaccine decision-making in this community, hampering the quality of consent given.

Analysis of the levels of confidence in participants' knowledge showed that those participants who had received information from council nurses had more confidence in their decision making about vaccines than those whose main source was their general practitioner. This highlights a need for patients and general practitioners to partner with these valuable community nurses to enhance patient education and confident decision-making.

Material risks with respect to immunisation in Islam

As Young states: "In a health-care setting, when a patient exercises her autonomy, she decides which of the options for dealing with her health-care problem (including having no treatment at all) will be best for her, given her particular values, concerns and goals." [12] Practicing Muslim patients place great value on the consumption only of those things deemed "halal" (ritually clean) and avoiding those things which may be unclean ("haram"). Pork is considered ritually unclean in Islam; and if a particular intervention contained pork-derived materials, this could reasonably constitute a material risk to a Muslim patient. [13] For example, in the British context, in a study of Muslim patients, 42% indicated that they would not take any medical interventions unless they were sure it was halal. [14]

Various vaccines, including MMR and the Hib vaccines, compulsory for Muslim pilgrims undertaking the Hajj [15] contain or involve porcine products in their manufacture, and are thus technically unclean. However, Islamic judicial and medical bodies embracing the value of beneficence have created an exemption for such products in the interests of public health. [16] The British statistics, as well as the findings of our study demonstrate that practicing Muslim patients harbour concerns about the halal nature of vaccines, and as such doctors need to be aware of concerns surrounding the prohibition and be able to effectively communicate the facts and exemptions of vaccine composition and manufacturing. This should include the referral of a patient on to more comprehensive sources should the need arise.

Conclusion

This investigation was undertaken to explore decision-making

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around immunisation. Our study of this Islamic school community clearly demonstrated a perceived information gap with the information presented surrounding vaccinations and a consequent lack of confidence in their decision-making process. Qualitative and quantitative feedback obtained in this study provided evidence that the current information provided on vaccination is not catering to the needs of this Islamic community.

One limitation of our investigation was lack of access to a non-Islamic control group as a point of reference for the broader Australian community's attitudes and knowledge. A broader information base would have clarified components of vaccine education generic to all communities and allowed tailoring education programs to the needs and concerns of individual communities. With respect to the Muslim community, there is scope for further inquiry into attitudes and awareness of general practitioners and nurses about the halal status of immunisations and other medical interventions, to triangulate the data and provide a basis for enhanced vaccine provider education.

The present study, however, provides evidence to encourage an increased role for council nurses in parental vaccine education, as well as identifying the desire of some Muslim parents for education on and confirmation of the ritual cleanliness of vaccines. By taking the time to inquire about and educate parents on all material risks, health professionals ensure confident, informed decision-making on the part of parents and a safe, healthy future for our children.

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Conflicts of interest

None declared.

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Recognition and response to the clinically deteriorating patient

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Background: Early recognition of clinical deterioration has been associated with a lower level of intervention and reduced adverse events. A widely-used approach in Australia is the Medical Emergency Team (MET) system. Research suggests having a multi-faceted approach to patient monitoring such as Modified Early Warning Score (MEWS) improves early review. **Aim:** To assess MET call initiation and response. **Objectives:** (1) In adult patients who have a MET call, was the call made immediately after meeting MET criteria? (2) In adult patients who have a MET call, was a MEWS scored > 4 reached prior to the call? **Methods:** 20 adult patients (> 18 years) that had a MET call made on acute medical or surgical wards at a Western Australian outer metropolitan secondary teaching hospital between 1 January and 30 April 2011 were selected. Records and observations were reviewed to determine whether MET call response was made immediately, and if MEWS were used, whether earlier review may have occurred. **Results:** Adjusted MET call response times (observations < 180 minutes) revealed 20% of patients did not have MET call made immediately (< one minute) and did not meet the standard. Ten percent warranted an earlier MET call and 25% achieved MEWS criteria > four within 180 minutes before MET call. Identification and responding to the patients with MEWS > 4 may have prevented 25% of MET calls. **Conclusion:** While all MET calls should have an immediate response, this is not always achieved. Implementation of MEWS may improve recognition and response to the deteriorating patient.

Introduction

Early recognition of clinical deterioration, followed by prompt response is associated with a lower level of intervention to stabilise patients and reduced adverse events. [1-3] Effective recognition and response to deterioration requires defined observation parameters, trained staff, appropriate equipment, policies, escalation protocol, communication and rapid response. [4] Adverse patient outcomes impact on the patient and health system, such as increased length of stay, unplanned return to theatre, increased morbidity, mortality, decreased bed availability and inefficient re-allocation of limited health resources. [5,6]

Early recognition and warning systems aim to identify and intervene before a patient deteriorates, reducing adverse outcomes. A widely-used approach in Australia is the Medical Emergency Team (MET) system, which includes staff education of the dangers of physiological instability, defining MET call criteria, improving communication and establishing policies, procedures, and systems for immediate response to patient deterioration. [7]

This study was conducted at a Western Australian outer metropolitan secondary teaching hospital (de-identified for publication and referred to herein as "health service") to look at recognition and response to the clinically deteriorating patient. The health service uses the MET call system. According to MET Call Policy [8], calls should be made as soon as a patient meets any MET call criterion (Figure 1). An internal audit [9] looked at observation tools, adherence to protocol, documentation and response. Results revealed 62.5% of patient deterioration were recorded and 25% of deterioration were not acted upon (i.e. no MET call or escalation for review). In addition multiple forms were used to record observations, resulting in gaps on charts, reducing the ability to identify trends. These findings are similar to a randomised



controlled study where the MET call system was introduced in twelve of 23 Australian hospitals. Researchers [7] found that when there were documented physical abnormalities and MET call criteria were reached, MET was called for only 30% of patients prior to unplanned intensive care unit (ICU) admissions. Furthermore, the MET system increased emergency team calling but did not substantially alter occurrence of cardiac arrest, unplanned ICU admission or unexpected death.

According to MET Call Policy, a MET call is to be made as immediately as possible when a patient falls within any one or more of the following criteria:

- Airway: Threatened
- Breathing: Respiratory rate < 8 or > 30 per minute
- Circulation: Pulse rate < 40 or > 130 beats per minute
- Systolic Blood Pressure: < 90 mm Hg
- Neurology: Sudden fall in level of consciousness (fall in GCS of > 2 points)
Repeated or prolonged seizures
- Urinary Output: Unexplained fall to < 100 mL over 3 hours
- Pulse Oximetry: Oxygen saturations < 90 % despite oxygen administration
- Other: Any patient who you are seriously concerned about that does not fit the above

Figure 1. MET / Code Blue Medical Emergency Calling Criteria (Adult). [10]

The Australian Commission on Safety and Quality in Healthcare has identified recognising and responding to clinical deterioration as a key issue. [4] The health service was introducing the COMPASS Modified Early Warning Score (MEWS) System (Figure 2 for calculation and Figure 3 for response). [12] Researchers reviewed outcomes of COMPASS and concluded that having a multi-faceted approach to patient monitoring improved early medical review following clinical instability. [11] The COMPASS system was being implemented to consolidate recordings and allow for a score (MEWS) to be calculated to flag early deterioration in addition to existing MET call processes.

The topic was chosen to enhance understanding of METs and early warning systems, including impact on outcomes and compliance with

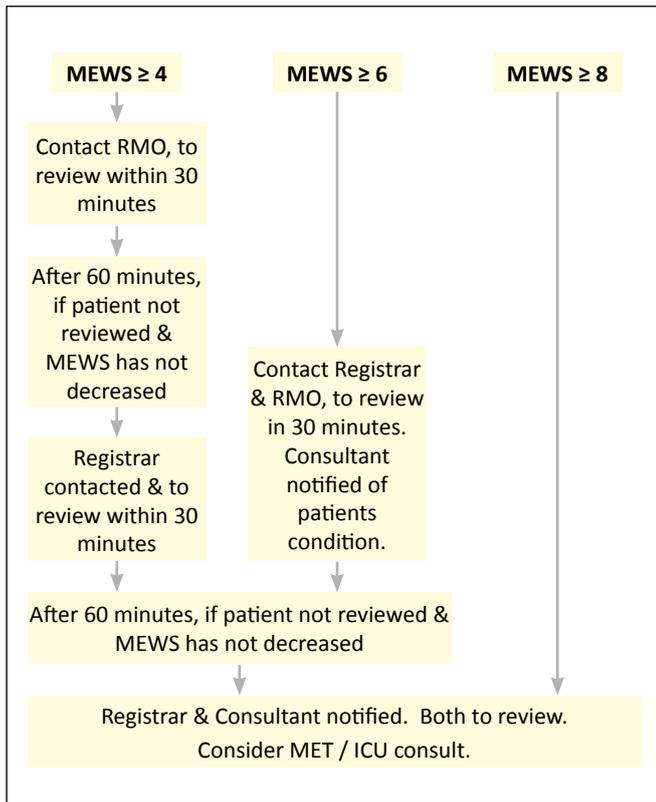


Figure 3. Modified Early Warning Score (MEWS) Response / Activation Protocol. [14]

MET policy. The aim was to assess MET call initiation and response (process of care).

Objectives:

1. In adult patients who have a MET call, is the call made immediately after meeting MET criteria? (Compliance with policy).
2. In adult patients who have a MET call, was MEWS > 4 reached prior to the call? (MEWS > 4 requires medical review which may prevent MET call).

Methods

Setting

A Western Australian outer metropolitan secondary teaching hospital with a total of 13,070 medical and 4,558 surgical admissions in 2011 (average 1,089 medical and 380 surgical admissions per month). On general surgery areas, there is medical cover during the day and an on call consultant 24 hours. On general medical areas, there is medical cover during the day, Resident / Registrar cover after hours until 22:00 and on call consultant 24 hours. Emergencies on both wards are covered by the MET. The health service has one MET and one backup team.

Standard

The MET Call Policy is the standard for MET calls (Figure 1). [8] One hundred percent of MET call cases must have a documented response immediately after an observation that meets MET call criteria (Figure 1).

There is Level III-1 NHMRC evidence for MERIT Study Investigators who found MET calls were made for 30% of patients before unplanned

To obtain the total MEWS, each individual observation below is scored:

MEWS	3	2	1	0	1	2	3
Respiratory Rate (per min)	<8			9-20	21-30	31-35	>36
SpO2 (%)	<84	85-89	90-92	>93			
Temperature (°C)	<34	34.1-35	35.1-36	36.1-37.9	38-38.5	>38.6	
Heart Rate (per min)	<40		40-50	51-99	100-110	111-130	>130
Blood Pressure*							
Sedation Score				0-1	2	3	4
Urine for 4 hrs or	<80 or	80-119 or		120-800 or	>800 or		
Urine for 24 hrs	<480	480-714		720-4800	>4800		

* See below (Document usual known Blood Pressure)

Usual SBP	190	180	170	160	150	140	130	120	110	100	90	80
200s	0	0	1	1	2	2	2	3	3	4	5	5
190s	0	0	0	1	1	1	2	2	3	3	4	4
180s	0	0	0	0	0	1	1	2	2	3	3	4
170s	1	0	0	0	0	1	1	2	2	3	3	3
160s	1	1	0	0	0	0	0	1	1	2	2	2
150s	1	1	1	0	0	0	0	0	1	1	2	2
140s	2	1	1	1	0	0	0	0	0	1	1	1
130s	2	2	1	1	0	0	0	0	0	0	0	1
120s	2	2	2	1	1	0	0	0	0	0	0	0
110s	3	2	2	2	1	1	0	0	0	0	0	0
100s	3	3	3	2	2	2	1	1	0	0	0	0
90s	4	3	3	3	2	2	2	2	1	1	0	0
80s	4	4	4	4	4	4	4	4	4	4	1	0
70s	4	4	4	4	4	4	4	4	4	4	4	4

Figure 2. Adult COMPASS Modified Early Warning Score (MEWS) Calculation. [13]

intensive care admission and equivocal improvements in outcome based on MET call alone. [7] There is Level III-3 NHMRC evidence for findings on the effectiveness of COMPASS. [11]

Case Definition

A case is any adult patient (> 18 years) on the acute medical or general surgical ward at the health service that had a MET call made between 1 January and 30 April 2011.

Patient Selection

MET calls are documented in the medical record. The Resuscitation Educator maintains a log of all MET calls. Only MET calls that occurred in patients aged 18 years and over on acute medical or surgical areas were chosen. In patients with multiple MET calls in one admission only the first MET call was reviewed and patients with altered MET criteria were excluded. A sample size of 20 was selected due to time constraints in reviewing multiple forms and calculating MEWS by transcribing observations using a collection tool.

Sample Size and Analysis

A pilot study was conducted on three records from March 2011. Descriptive data were used for analysis. Confidence intervals (CI) were calculated using the modified Wald method. [15]

Data Collection

Data were obtained from medical records selected as per Patient Selection. The MET calls log was obtained for 1 January to 30 April 2011. MET calls for non-medical and non-surgical patients, patients less than 18 years and piloted records were removed. The first 20 MET calls where medical records could be located were chosen.

The Author collected data by reviewing medical records and records checked for altered MET criteria statements. Observations < 180 minutes to the MET call were checked on all forms in the admission. Within 180 minutes was chosen, as MET call criteria requires urine output over 3 hours to be checked. MEWS was calculated to the observation greater than but closest to 180 minutes before the MET call using MEWS Collection Tool. Data were entered into Microsoft Excel using data collection tool and dictionary. Demographic, exposure and outcome variables are listed in Figure 4. Missing, conflicting and ambiguous data were recorded as 'missing'.

Other Issues

Cases were de-identified. Electronic data were password protected and collection tools stored securely. Identifying staff and patient information were not recorded, patient interaction was not required and patient consent was not necessary as per NHMRC. [16] Stakeholders included staff involved in initiating or attending METs and Executive. Clinical Quality and Safety Committee approval was obtained.

Results

Twenty of the 36 adult medical and surgical patients who had MET calls during January to March 2011 were selected (55.6% of MET calls). Age range of patients selected was 29 to 89 years, with a mean age of 74.7 years (median 79 years). In comparison, age range for the 36 patients from which patients were sampled was 29 to 92 years, with a mean age of 72.3 years and median 77.5 years. There were no patients with altered MET criteria.

Reason for MET call is summarised in Table 1. Five patients (25%) achieved two MET call categories, while no patients reached three or more categories. The most common reason for MET call was circulation problem (i.e. pulse rate < 40 or > 130 beats per minute (bpm)), with seven patients (35%) having MET call for this reason.

MET call response times varied between zero and ten minutes (Figure 5). Seventeen patients (85%) had a response within and including one minute. Three patients had a delay exceeding one minute (15%). The mean response time was one minute and median zero minutes.

Two patients (10%) were identified as reaching MET call criteria in

Demographic / Exposure Variables:

1. Unique identifier	For case identification, data consolidation and prevention of duplication.
2. Date of birth	Patient inclusion > 18 years at time of MET call.
3. Date and time of MET call	Exactly when the MET call occurred.
4. Date and time of observation resulting in MET call	Exactly when the observation was documented that initiated the MET call.
5. Did patient have an earlier observation < 180 minutes warranting MET call before the observation that resulted in the MET call?	Establishes whether there was an earlier observation where a MET call should have been made in the preceding 180 minutes.
6. Was MEWS > 4 reached < 180 minutes before the MET call was made?	Establishes whether under the proposed COMPASS system if the patient would have been identified as requiring MEWS response (i.e. Score > 4). MEWS response may prevent MET call.
7. Discharge date	Date of discharge.
8. Discharge destination	Discharge disposition. Determines whether the patient was discharged home, died or was transferred to another hospital.

Outcome Variables:

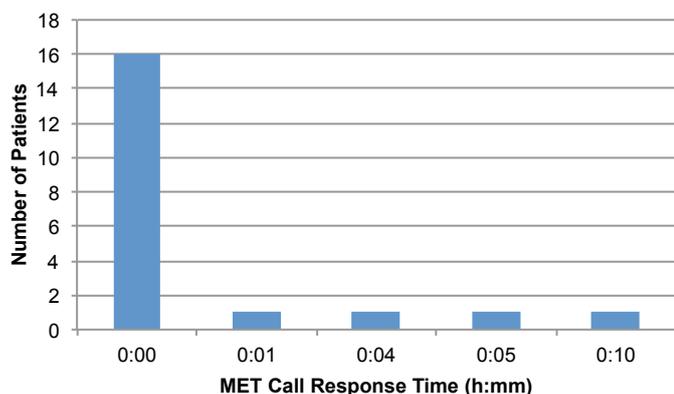
MET call response time (formula / calculation)	Time between observation resulting in MET call and when the MET call was made. I.e. Time in minutes calculated as [Date + Time of MET call] minus [Date + Time of observation resulting in MET call]
Delayed MET call response time (formula / calculation)	Time between the deviated observation that should have initiated a MET call and when the MET call was made. I.e. Time in minutes calculated as [Date + Time of MET call] minus [Date + Time of deviated observation warranting MET call]
MEWS time (formula / calculation)	Time between the earliest calculated MEWS > 4 (closest to but > 180 minutes before MET call) and when the MET call was made. I.e. Time in minutes calculated as [Date + Time of MET call] minus [Date + Time of earliest MEWS > 4]
Post-MET Length of Stay (formula / calculation)	Days between date of discharge and date of MET call. I.e. Post-MET LOS calculated as [Date of discharge] minus [Date of MET call]

Figure 4. Data collection domains.

Table 1. Reason for Medical Emergency Team (MET) Call.

MET Category (Primary)	MET Category (Non-Primary)				Total	Percent
	SBP	Neurology	Other	One MET Criterion		
Airway	0	0	0	0	0	0%
Breathing	0	0	0	1	1	5%
Circulation	1	0	2	4	7	35%
SBP	0	1	1	3	5	25%
Neurology	0	0	0	5	5	25%
Pulse Oximetry	0	0	0	0	0	0%
Seizures	0	0	0	1	1	5%
Urine Output	0	0	0	0	0	0%
Other	0	0	0	1	1	5%
Total	1	1	3	15	20	
Percent	5%	5%	15%	75%		

MET Category relates to MET call criteria (Figure 1).

**Figure 5.** MET call response time.

observations before the one that resulted in MET call. The delay was 14 and 160 minutes, with an average of 87 minutes (Table 2). The patient with a 14 minute delay had a further four minute deferral after the second observation that achieved MET call criteria. The patient with 160 minute delay had the MET call made immediately after the subsequent observation that achieved MET call criteria. Consequently four patients (20%) had an adjusted MET call response time greater than one minute (mean 9.5 minutes, range 0-160 minutes, median 0 minutes, 95% CI 0.0749-0.4218).

Table 4. Post-Medical Emergency Team (MET) Call Length of Stay (LOS) and Discharge Destination.

Post-MET Call LOS (Days)	Discharge Destination						Total
	At own risk	Deceased	Home	Mount Hospital	Royal Perth Hospital	Sir Charles Gairdner Hospital	
0		1			1	3	5
1	1		1				2
2			1	1			2
4			2				2
5		1	1				2
6			1				1
7			1				1
>7			4		1		5
Total	1	2	11	1	2	3	20

Table 2. Delayed Medical Emergency Team (MET) Call Response Time.

Delayed MET Call Response Time (Hours)	No. of Patients
0:14 (14 minutes)	1
2:40 (160 minutes)	1
No earlier observation meeting MET call criteria	16
Data Missing	2
Total	20

Delayed MET Call Response Time: Time between the earlier observation that should have warranted a MET Call and when the call was made.

For two patients (10%), it could not be determined whether an earlier observation fell into MET call criteria. One patient had missing progress notes and observation chart. The other had documented deviated observations in the progress notes without time recorded. It could not be ascertained whether this occurred within 180 minutes of the MET call.

Five patients (25%) achieved a calculated MEWS > 4 within the last observation greater than but closest to 180 minutes of the MET Call (Table 3). The 95% CI extends from 0.1081-0.4725. Of these, four were < 180 minutes of the MET call. Time period between MEWS > 4 and MET call ranged between five and 210 minutes (3 hours 30 minutes), with a mean of 113 minutes.

Table 3. Modified Early Warning Score (MEWS) Time.

MEWS > 4, Time (Hours)	No. of Patients
0:05	1
1:15	1
1:55	1
2:40	1
3:30	1
MEWS < 4	14
Data Missing	1
Total	20

MEWS Time: Time between when MEWS Score was > 4 and when the MET Call was made.

Five patients (25%) were discharged the same day as the MET call (Table 4). Of the five patients, one patient deceased (5%) and four patients (20%) were transferred to an acute hospital for further management (i.e. Royal Perth or Sir Charles Gairdner Hospitals).

Discussion

Adjusted MET call response times (inclusive of observations < 180 minutes) revealed 20% of patients did not have MET call made immediately (< one minute) and did not meet the standard. Ten percent

warranted an earlier MET call and 25% achieved MEWS criteria > four within 180 minutes before MET call. Identification and responding to the patients with MEWS > 4 may have prevented 25% of MET calls. The CI of 0.1081 to 0.4725 warrants further study with increased sample size.

Twenty percent may not have met the standard due to delayed MET call response (e.g. hesitation or watchful waiting), inexperience, not recording altered MET criteria, and inaccurate documentation of times on the Resuscitation Record. The Resuscitation Record contained pulse rate > 140 bpm whereas hospital policy states pulse rate > 130 bpm warrants MET call. While this did not appear to affect data, it may create confusion for staff.

Ten percent of patients required earlier MET call, showing an improvement to a previous audit [9] where 25% of deterioration were not acted upon. While not achieving the standard, results are better than those found by MERIT Study Investigators where only 30% of patients admitted to the ICU had a MET call. [7] This study looked at various patients, not just ICU admissions which may contribute to this variance. Besides revealing current practice, the study provides a baseline for evaluation of COMPASS and effectiveness of MEWS post-implementation in achieving the standard.

Twenty-five percent of patients were discharged on the same day as the MET call. One patient who achieved a MEWS > 4 was discharged the same day and earlier identification with MEWS may have allowed for earlier planning or transfer. The deceased patient had an unpreventable condition.

Limitations:

- Patients without MET call may have reached calling criteria. These were not included as the audit looked at MET calls made. Failure to meet the standard may be higher.
- Observations in the preceding 180 minutes were reviewed. Patients may have had observations warranting MET call earlier than this.
- Not all observations used in MEWS calculation were recorded in every observation set. MEWS > 4 may have been reached yet could not be determined.
- Adult surgical and medical patients were included. Responses for other groups may differ.
- Sample was determined from the MET call log. Missing forms or accidental omissions during logging of cases may have affected accuracy.
- Audit period included January which may include increased agency and relief staff. This was intentional as staff should respond to and be familiar with MET call processes.
- Patients with multiple MET calls only had the first MET call reviewed.

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- This was a single site and results may not be externally valid.
- While data collected by the author was pre-recorded in the medical record, the author was not blinded to the study aims.

Results, feedback and recommendations were communicated with stakeholders at the health service through a summary report which was distributed by email, followed by presentation of findings and feedback session. Recommendations were as follows:

- Record observations on a single form.
- MET call policy requires a definition of “immediate” (e.g. less than one minute) to provide clarification and measurable outcome.
- Reiterate to staff the importance of accurate documentation (e.g. times).
- Conduct research to assess patient outcomes and compare with other hospitals.
- Re-audit following MEWS Observation Chart implementation. Compare MET call response with other Australian hospitals that utilise COMPASS.
- Obtain further stakeholder feedback on existing practice and potential for improvement (e.g. verbal discussion, email, team meetings).
- Adjust pulse rate on the Resuscitation Record to > 130 bpm to reflect hospital policy.

Recommendations may be applicable to other health services utilising MET call system and MEWS, particularly defining what “immediate response” is with a timeframe to allow for review of compliance. Further research could review a selection of patients regardless of whether MET call was made and review observations to determine whether MET call should have been made. While this is a time consuming task, hospitals utilising MEWS charts will make this process easier.

Conclusion

While all MET calls should have an immediate response, this is not always achieved. Implementation of MEWS or secondary warning system may improve recognition and response to the clinically deteriorating patient. Responding to a patient at an early stage in their deterioration may reduce adverse outcomes and use of resources. To improve review and audit of response to clinical deterioration, further clarification of what “immediate” means is required in the standard.

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Conflict of interest

None declared.

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Vitamin D deficiency in the elderly: How can we improve rates of screening and supplementation in General Practice?

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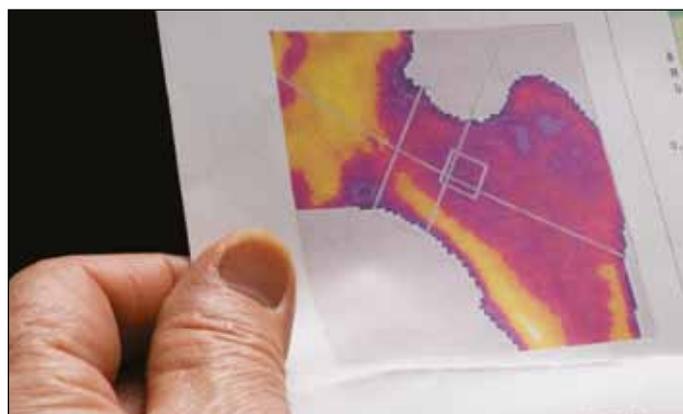
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Aim: Vitamin D supplementation reduces falls and fractures in the elderly, yet screening and supplementation rates are generally inadequate. We therefore investigated whether rates of screening and supplementation could be improved through a brief, general practitioner (GP)-focussed, educational intervention. **Methods:** Clinical audits of vitamin D screening and supplementation in elderly patients attending a rural general practice were conducted before and after a GP educational intervention. **Results:** The simple GP educational intervention resulted in both vitamin D screening (11.1% versus 5% - 2 year period; and 6.11% versus 3.38% - 3 month period) and supplementation rates ≥ 700 IU cholecalciferol daily (10% versus 5% - 2 year period; and 4.44% versus 0.97% - 3 month period) approximately doubling in elderly patients. **Discussion:** This preliminary study suggests that simple, cost-effective GP-focussed interventions can significantly improve vitamin D screening and supplementation rates in elderly patients, thereby potentially improving health outcomes in terms of falls and fractures in this 'at risk' population.



but larger doses are needed for those who are deficient. [7] Deficiency should be treated with 3000 to 5000 IU cholecalciferol daily for four to twelve weeks, reducing to 1000-2000 IU daily for maintenance therapy. [7,8] No evidence of toxicity has been found in doses of up to 4000 IU daily. [7]

Introduction

Over 30% of the elderly population fall annually, and many suffer from multiple falls. [1] Falls result in decreased physical activity, possible loss of independence and a fear of falling, as well as being the leading cause of hospitalisation and death in the elderly. [1] Healthcare costs for fall-related injuries are expected to double over the next few years due to the ageing population. [1]

Recent studies have linked vitamin D deficiency to an increased risk of falls and fractures in the elderly. [2, 3] It is thought that vitamin D decreases falls by increasing muscle strength and balance, and reduces fractures by increasing bone strength. [2, 3] This is an important finding given that between 45% and 75% of Australian elderly patients have been diagnosed as vitamin D deficient. [4] Many of these patients have become vitamin D deficient because of reduced sunlight exposure or a reduced ability to synthesise vitamin D from ultraviolet exposure. [1] Other contributing factors include diet [5], malabsorption, medications, renal and/or liver impairment. [5, 6]

Vitamin D deficiency can be detected using the 25-hydroxy vitamin D radioimmunoassay. Although target ranges are debated, concentrations of serum 25-hydroxy vitamin D above 75nmol/L are considered sufficient; 50-75 nmol/L suboptimal; 25-50 nmol/L insufficient; 15-25 nmol/L deficient and < 15 nmol/L severely deficient. [7] Daily requirements for vitamin D are around 800-1000IU to prevent falls,

A recent meta-analysis of eight randomised controlled trials (RCTs) involving 2426 patients with a mean age ≥ 65 years showed that supplemental vitamin D in the range of 700-1000IU elevated vitamin D levels to 60-95nmol/L and reduced falls by nineteen percent within two to five months of commencement of treatment. [9] Similarly, these larger doses were found to reduce the incidence of fractures in the elderly, as shown in a meta-analysis of twelve double-blinded trials involving 83165 patients (> 65 years of age), receiving doses of between 482-770IU of cholecalciferol daily, which reduced hip fractures by eighteen percent and non-vertebral fractures by twenty percent. [10] Notably however, in some studies where patients were given approximately 700IU vitamin D supplementation without initially recording their serum vitamin D level, they did not gain sufficient vitamin D levels [9,11,12], potentially because they were initially vitamin D deficient. [11] This is supported by a study that found vitamin D deficient patients with a mean baseline of 25nmol/L, when given suboptimal therapy with either 600IU daily, 4200IU weekly or 18000IU monthly, had vitamin D levels below 75nmol/L after a four month follow-up (63% of the daily group versus 72% of the weekly group versus 96% of the monthly group). [13] It seems logical therefore to measure vitamin D levels before prescribing appropriate vitamin D supplementation, even though current recommendations suggest that elderly patients should be given vitamin D supplementation with or without screening. [4,6,14] Interestingly, a RCT comparing vitamin D

supplementation with and without baseline Vitamin D screening has never been performed. [15]

While the above literature indicates a growing problem with vitamin D deficiency in elderly Australian patients, [4] which is linked to morbidity and mortality, [1] there is currently a lack of research examining the feasibility of improving rates of vitamin D screening and supplementation in general practice. The aims of this study were therefore: 1) To evaluate documented vitamin D screening and supplementation rates of elderly patients (≥ 70 years) attending a rural general practice, and 2) To evaluate the impact of a brief intervention aimed at increasing GP's knowledge about vitamin D screening and supplementation at doses ≥ 7000 IU cholecalciferol daily to prevent falls and fractures in the elderly. [9,10]

Methods

The research protocol was reviewed and approved by the University of Wollongong Human Research Ethics Committee. Relevant de-identified data were collected from the medical records of 387 patients, aged ≥ 70 years, who had recently attended a rural health practice in western New South Wales. All five GPs working in the practice volunteered to participate in the study.

Pre-intervention

A pre-intervention audit was conducted on the medical records of all elderly patients (> 70 years of age) attending the practice from the 1st September to 1st December 2009, determining documented rates of 1) Measurement of serum vitamin D and 2) Vitamin D supplementation.

Intervention

The student researcher (the primary author) delivered a one hour education session to the GPs about the importance of vitamin D in preventing falls and fractures in the elderly, and discussed best practice guidelines for treating vitamin D deficiencies (Table 1). [8] Following the education session, a reminder was attached to individual GP computer screens, stating: 'Is your patient over 70? Have you checked their serum vitamin D level lately?'

Table 1. Key messages delivered in the GP educational session which formed part of the current intervention.

Key Messages	Details
1) The role of vitamin D in maintaining health and wellbeing.	Adequate vitamin D levels help to decrease falls by increasing muscle strength and balance, and reduce fractures by increasing bone strength. [2,3] Vitamin D also protects against cardiovascular problems, oncogenesis, autoimmune disease, neuro-degeneration and cognitive decline. [5]
2) Risk factors for vitamin D deficiency.	Age >65 years, dark skin, obesity, insufficient sunlight exposure, medication use (e.g. anticonvulsants, glucocorticoids). [21]
3) Signs and symptoms of vitamin D deficiency.	Bone pain in lower extremities, muscle pain and weakness, increased risk of falls. [22]
4) Classification of vitamin D deficiency.	Sufficient >75 nmol/L 25-OH; Suboptimal = 50-75 nmol/L 25-OH; Insufficient = 25-50 nmol/L 25-OH; Deficient = 15-25 nmol/L 25-OH; Severely deficient < 15 nmol/L 25-OH [7]
5) How to treat vitamin D deficiency.	Cholecalciferol 125 micrograms (5000 IU) orally, daily for four weeks, then reduce to 25 to 50 micrograms (1000 to 2000 IU) daily, as long as required. [8]

Post-intervention

A post-intervention audit of the medical records was conducted examining the same dependent variables, on all elderly patients (> 70 years) who attended the practice during the three month post-intervention period (18 January-18 April 2010).

Analysis

Two year rates of documented screening for vitamin D levels, and rates of supplementation at ≥ 7000 IU cholecalciferol daily were compared between patients attending the practice in the three month period pre-intervention and those attending in the three month period post-intervention. Two year rates were chosen as these data were easily accessible from the medical records, and the majority of previous studies have considered similar time periods. [9,10,11] Additionally, because the two year rates for the post-intervention sample overlapped with the pre-intervention period, a second comparison was made for three month rates of screening and supplementation rates pre and post-intervention. Chi-squared tests were used to examine statistical significance.

Results

In the three month pre-intervention period, 207 elderly patients (≥ 70 years of age) attended the practice, and their records were used for the pre-intervention audit. During the three month post-intervention period, 180 patients (>70 years of age) attended the practice, and their records were used for the post-intervention audit. In the pre and post-intervention audits, two year rates, as well as three month only rates of vitamin D screening and supplementation were calculated. The rates for screening of vitamin D deficiency approximately doubled in both the two year, and three month measures, with a 5% (11) two year screening rate before the intervention and an 11.1% (20) rate after the intervention; as well as a 3.38% (7) three month screening rate before the intervention and a 6.11% (11) after the intervention (Figures 1 and 2). Similarly, two year rates of supplementation at ≥ 7000 IU cholecalciferol doubled from pre to post-intervention audit (5% (11) pre versus 10% (18) post), and three month rates increased fourfold (0.97% pre versus 4.44% post) (Figures 1 and 2).

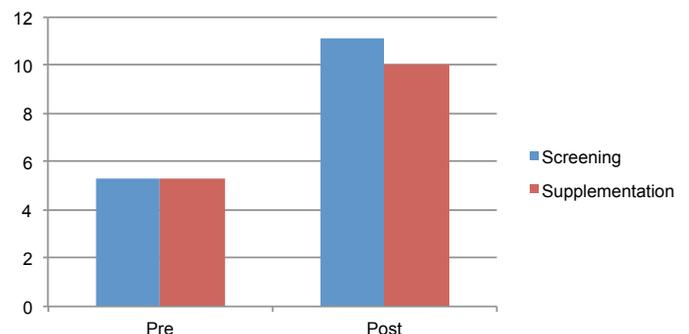


Figure 1. Two year rates (percentages) of elderly patients' records indicating screening and supplementation at ≥ 7000 IU cholecalciferol in the pre and post-intervention audits.

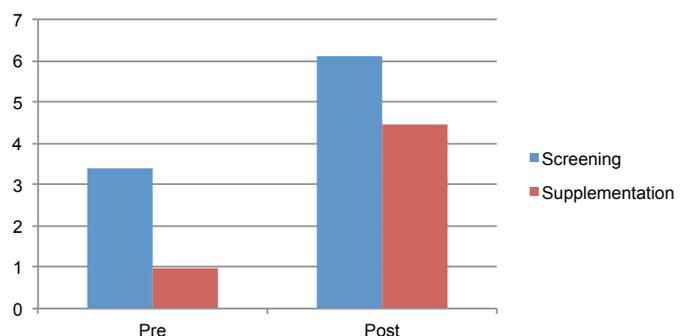


Figure 2. Three month rates (percentages) of elderly patients' records indicating screening and supplementation at ≥ 7000 IU cholecalciferol in the pre and post-intervention audits.

Chi-square analyses of these results found that the difference was statistically significant for two year rates of screening, $\chi^2 (1) = 5.05$, $p < 0.05$, and for supplementation at $\geq 700\text{IU}$ cholecalciferol daily $\chi^2 (1) = 4.39$, $p < 0.05$, suggesting that improvements are unlikely to have occurred by chance. In the three month pre-post comparison, there were non-significant trends towards improvements in screening and supplementation in the post compared to pre-intervention group. The lack of significance was probably due to small participant numbers in the three month comparison.

Tables 2 and 3 show vitamin D levels and supplementation doses for screened patients in the pre and post-intervention audits. In the pre-intervention audit, no screened patients were taking $\geq 700\text{IU}$ cholecalciferol doses daily. In the post-intervention audit, both two year (Table 2) and three month (Table 3) rates of documented $\geq 700\text{IU}$ cholecalciferol doses had increased to 35% and 63% respectively of screened patients.

Discussion

This preliminary study clearly indicates that simple interventions such as increasing GP awareness of the importance of screening and supplementation for vitamin D deficiency in elderly patients, and reminders, can help to improve clinical practice and potentially the health outcomes for elderly patients. The majority of elderly patients (71-82% pre and 90-91% post-intervention) screened had suboptimal-deficient levels of vitamin D according to clinical guidelines, [7] supporting the importance of screening and supplementation in this 'at risk' elderly patient population. Following the intervention, documented rates of screening and supplementation at doses of $\geq 700\text{IU}$ cholecalciferol daily in elderly patients increased significantly in this small study. The intervention may have worked through increasing GPs' knowledge base regarding the importance of vitamin D screening and supplementation, optimal rates of supplementation, and through the ongoing reminder to check these in elderly patients. Busy clinicians are likely to find it difficult to keep up to date with research and treatment developments, and the current study highlights the potential benefits of medical student projects to GPs and communities. Simple interventions, such as those used here, therefore show promise as they are inexpensive, brief and highly effective, approximately doubling the rates of documented screening and recommended dosing of vitamin D supplementation at $\geq 700\text{IU}$ cholecalciferol daily in a brief (three month) period.

The results of this preliminary study also highlight the need for further improvement. Although documented screening rates and doses of $\geq 700\text{IU}$ cholecalciferol daily doubled post-intervention, only 6.11-11.1% of elderly patients were being screened and 4.44-10% were receiving doses demonstrated to prevent falls in the elderly. Further research is needed to help determine barriers to adequate vitamin D screening and supplementation rates. These may include time constraints on busy GPs, the expense of vitamin D assay or elderly patients not being able to afford vitamin D supplements which are not subsidised by the Pharmaceutical Benefits Scheme (PBS). It must also be noted that in the present study, many elderly patients did not have their vitamin D levels tested, making it impossible to determine whether $\geq 700\text{IU}$ cholecalciferol daily was an effective therapeutic dose, because those who are vitamin D deficient require larger doses. [8,9,10,16] It is also possible, given the increased rates of supplementation post-intervention, that GPs moved straight to supplementation without screening. It may be that the low risk of toxicity with vitamin D supplementation and the serious health implications of deficiency in the elderly led GPs to begin supplementation without any inconvenience or expense associated with the blood test. Further research could examine GPs' views about these issues.

In addition to the simple, cost effective intervention piloted in this study, broader strategies that may be useful in increasing screening and supplementation could include the addition of serum vitamin D measurement to the Medicare funded 'over 75 health' assessment, [17] and adding vitamin D supplements to the PBS. Further investigations would need to be carried out to evaluate whether these additional measures could also help to improve rates of screening and supplementation, thereby potentially preventing falls and fractures in the elderly.

Limitations of the study include the small number of records audited from a single medical practice, a short data collection period, reliance on documentation in patient records and the possible use of over-the-counter vitamin D supplements which were not documented in the patient notes. Further, rates of calcium supplementation were not assessed. A recommended daily 1300mg calcium supplementation, [8] together with vitamin D, has a combined effect on preventing falls and fractures in the elderly. [18,19,20] These factors warrant further research.

In conclusion, the results of this preliminary study indicate that a brief GP-targeted educational intervention is an effective way of improving

Table 2. Two year Vitamin D and supplementation levels in screened patients in the pre and post-intervention audits.

Serum vitamin D levels	Pre-intervention		Post-intervention	
	Number of patients (% of those screened)	Taking $\geq 700\text{IU}$ cholecalciferol daily	Number of patients (% of those screened)	Taking $\geq 700\text{IU}$ cholecalciferol daily
Sufficient	2 (17%)	0	2 (10%)	0
Sub-optimal	5 (42%)	0	12 (60%)	6 (30%)
Insufficient	4 (33%)	0	6 (30%)	1 (5%)
Deficient	1(8%)	0	0	-
Total	12	0	20	7 (35%)

Table 3. Three month Vitamin D and supplementation levels in screened patients in the pre and post-intervention audits.

Serum vitamin D levels	Pre-intervention		Post-intervention	
	Number of patients (% of those screened)	Taking $\geq 700\text{IU}$ cholecalciferol daily	Number of patients (% of those screened)	Taking $\geq 700\text{IU}$ cholecalciferol daily
Sufficient	2 (29%)	0	1 (9%)	0
Sub-optimal	2 (29%)	0	7 (64%)	4 (36%)
Insufficient	3 (42%)	0	3 (27%)	3 (27%)
Deficient	0	0	0	0
Total	7	0	11	7 (63%)

documented rates of vitamin D screening and supplementation in the elderly.

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Conflicts of interest

None declared.

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Key points:

- Vitamin D deficiency, which can increase the number of falls and fractures, is common amongst older people
- Vitamin D screening and supplementation rates for older patients are often poorly documented by General Practitioners
- A simple education intervention targeted toward GPs can help improve the vitamin D screening and supplementation rates of older people

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Australia's experience of *Bordetella pertussis* and a proposed national preventive strategy into the future

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Elimination of *Bordetella pertussis*, an exclusively human pathogen, has proven to be elusive in Australia despite universal vaccination. Australia has witnessed a resurgence of pertussis particularly in infants less than 6 months old, and adults over 20 years old. This resurgence has resulted in high notification rates, morbidity and mortality in the two age groups. This may be due to the largely asymptomatic presentation in young infants and adults, as well as sub-optimal immunity due to lack of development, or waning immunity in adults. Various levels of prevention need to be identified so that a national preventative strategy may be sought to reduce the impact of pertussis infection amongst Australians in the future.

Introduction

Pertussis is an acute illness caused by *Bordetella pertussis*, a Gram-negative coccobacillus with exclusive affinity for the mucosal layers of the human respiratory tract. Pertussis is highly contagious and spread by air borne respiratory droplets when an infected person coughs or sneezes, or via direct contact with secretions from the nose or throat. [1] Following an incubation period of 9-10 days, patients usually present with an irritating cough that gradually becomes paroxysmal and lasts for 1-2 months. [2] However, in adults and older children, the diagnosis of pertussis is often subclinical and delayed due to an absence of classical symptoms, resulting in potential transmission of infection for several weeks. [3] In Australia, the preferred methods for laboratory diagnosis of pertussis are culture and polymerase chain reaction (PCR), and it is recommended in most cases that both tests be performed. However, there is a trend to move towards PCR, which provides rapid results, and is more sensitive in previously immunised individuals, and more likely to be positive in patients who have received antimicrobial treatment than culture. [1-4]

Since the 1950s, effective pertussis immunisation programs have reduced hospitalisations and deaths in Australia dramatically. [4] Currently, the acellular pertussis vaccine (DTPa) is safer and more effective than whole cell pertussis vaccine (DTPw), which is no longer used in Australia. [1] DTPa vaccines are associated with lower incidence of fever and local reactions than DTPw, and serious side effects are rare. [1,6] DTPa is free for Australian children at 2, 4 and 6 months of age, with a booster available at 4 years and during adolescence. [5] Despite the availability of vaccines in Australia, it remains a challenging disease to control among two age groups: under the age of 6 months who suffer the most severe infections and highest mortality, and those older than 20 years. [1,6] Adolescents and adults are an important reservoir for infection as they are capable of transmitting pertussis to infants who were too young to have received two or more DTPa vaccines required for optimum protection. [1]

Epidemiology

In Australia, pertussis cases are notifiable under each state and territory Public Health Act. [4] There were 34,490 pertussis notifications received by the National Notifiable Diseases Surveillance System (NNDS) in 2010, the highest recorded since 1991 (Figure 1). A general increase in endemic peaks have occurred every 4-5 years since national notifications became available in 1991, occurring in 1997 (12,232 notifications), 2001 (9,530 notifications), 2005 (11,168 notifications)

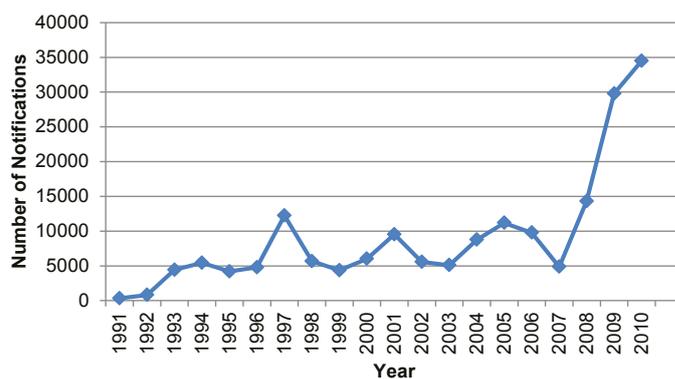


Figure 1. Pertussis notifications in Australia, 1991-2010. [7]

and 2010 (34,490 notifications). A clear seasonal pattern exists, with the highest number of notifications in the spring and summer months (between August and February) each year between 1993 and 2010. [2]

In terms of age specific pertussis incidence rates, children less than 1 year old had the highest annual notification rate in all of the analysed years, and high rates were also observed in 5-9 years olds, with a peak notification rate in 1997 of 194 cases / 100,000. [4] Adults aged 20-59 years accounted for 56% of notifications, with elderly patients aged 60 years and over accounting for 15% of notifications in 2005 (Figure 2). Recently, there has been a rise in notification rates in the 20-59 year old age group, and in those over the age of 60, increasing by 57% and 17% respectively in 2010. This is in contrast to the relatively steady annual rates previously seen in these age groups between 1993-2003.

Hospitalisations, which refer to a period of time when a patient is confined to a hospital, followed a similar pattern to notifications (Figure 1) with a total of 1,478 separations recorded during 1998-2008 (Figure 3). Of these separations, they were most prominent in the 0-4 age categories, with 967 separations (Table 1). Peak separations occurred in the period of 2001-2002 (258 separations), 2004-2005 (222 separations) and 2007-2008 (250 separations).

There were 9,338 hospital bed days recorded for all ages during 1998-2008, with the highest number of hospital bed days toward the 0-4 year old group. Total hospital bed stays peaked during 2001-2002 (1,628 days) and 2004-2005 (1,640 days). Over the two years 2003-

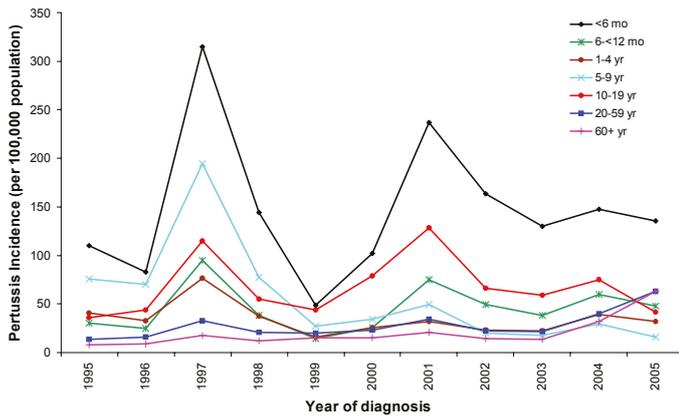


Figure 2. Pertussis notifications per 100,000 population by age group, 1993-2005. [4]

2004, two deaths were recorded where pertussis was the underlying cause, with both occurring in 2004; one case was 1 month of age and the other a 95 year old patient. [2] During 1993-2002, there was a total of 16 deaths attributed to pertussis, of which 15 (94%) occurred in infants less than 6 months of age. [6]

The latest study by Australian Department of Health and Ageing showed that between 2003-2005, only 37% of infants less than 6 months were fully vaccinated, and 12% partially vaccinated. [2,4] There are proposed explanations for increasing pertussis rates seen amongst infants in the less than 6 months of age group. Two or more doses of a pertussis-containing vaccine appear to be needed for protection, and infants less than 6 months of age are likely to be too young under Australian immunisation schedules to have reliably received two or more doses. [3] It is also likely that adults, particularly parents, are a significant source of infection to infants. Regarding individuals aged 20 and over, it is likely that increased notifications are related to greater use of serology as a diagnostic tool, and an ageing population. [4,8] Also, waning immunity following infant vaccination and reduced opportunities for boosting immunity due to reduced circulation of pertussis may also contribute to increased susceptibility to pertussis infection and disease in the 20 years and over population. [3,8]

Risk factors

Understanding the risk factors for pertussis infection is essential to target areas of concern, and to provide a skeleton for drafting a national preventative strategy. They include:

- Infants and children who are not immunised yet. In infants, the first dose of vaccine is immunogenic only from the age of 6 weeks, thus infants less than 6 weeks are at the highest risk of pertussis infection, often from the parents. [1-6]
- Infants under 12 months old. Infants are particularly prone to infection prior to receiving the first two doses of DTPa. Adolescents and adults are an important reservoir for infection as they are capable of transmitting pertussis to infants. [1] In addition to increased susceptibility of acquiring infection, infants are also

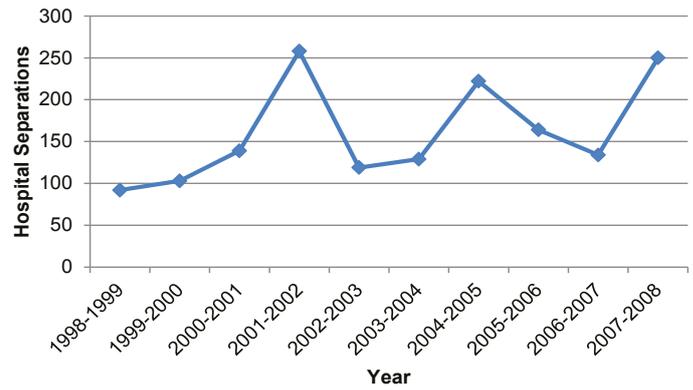


Figure 3. Pertussis hospital separations in Australia, 1998-2008. [7]

most at risk of developing severe complications, such as apnoea, bacterial pneumonia, pulmonary hypertension and cor-pulmonale. [5,10]

- Adolescents aged between 12-17 years. Immunity, whether from immunisation or past history of Bordatella pertussis infection, decreases after approximately 6-10 years, resulting in renewed susceptibility to infection. Thus for most adolescents, if they do not receive a booster shot during adolescence, they are at risk, as their last dose of DTPa would have been at 4 years of age in Australia. [1-3,7,9]
- Living in the same house or working in close contact with someone infected with Bordatella pertussis. Studies have demonstrated that households with members who have culture-positive Bordatella pertussis were more likely to have greater secondary spread. Hence, proximity is an important predictor of household and community-acquired infection, with adolescents being at higher risk compared with other age groups. [13] Additionally, adults working with young children, especially childcare workers and healthcare workers in contact with infected infants are at a higher risk of contracting *Bordetella pertussis* infection. [1]
- Persons with immunodeficiency and other underlying medical conditions. These include patients who have congenital or acquired immunodeficiency, cystic fibrosis, chronic heart failure, diabetes and chronic lung disease.
- Indigenous Australian Infants. One study demonstrated that 52% of pertussis hospitalisations in Indigenous infants occurred at 0-2 months of age, and rates in these indigenous infants were significantly higher in remote areas. Also, indigenous infants had higher hospitalisation rates and were more frequently delayed of vaccination than age matched non-indigenous infants. [14]

Prevention activities

When thinking about prevention in population health, there is consideration towards four types of prevention:

- Primordial Prevention: Avoid the emergence and establishment of 'upstream' factors such as social, cultural and economic factors that contribute to increased disease incidence.
- Primary Prevention: Preventing disease from occurring in the first place; to reduce the incidence of disease. [15]

Table 1. Pertussis separations, hospital bed days and average length of stay in period 1998-2008 and deaths in 2003-2004. [7]

Age Group (Years)	Hospital Separations	Hospital Bed Days	Average Length of Stay in Hospital (days)	Deaths 2 years (2003/2004)
0-4	967	6021	5.2	1
5-14	86	313	7.1	0
15-24	23	78	3.6	0
25-59	203	1129	5.43	0
60+	199	1797	9.07	1
All Ages	1478	9338	6.08	2

- Secondary Prevention: Reducing morbidity and mortality by improving the outcome of disease (such as early diagnosis and treatment) that has already developed. [15]
- Tertiary Prevention: Reducing the progress or complications of disease and implying better rehabilitation or quality of life in the longer term. [15]

Table 2 outlines how these different types of prevention could be implemented in Australia in the future.

A national preventative strategy

A national preventative health strategy requires effective health promotion programmes. Health promotion is the process of strengthening the capability of individuals to take action and the capacity of communities to act collectively to exert control over the determinants of their health. [19]

Program Planning

Target Populations: Epidemiological and demographic information suggests that infants aged less than 6 months are at the highest risk of severe pertussis disease due to partial immunisation. Also, there is an increasing number of notifications in adults aged 20 years and over. [1] These two age groups could be extensively targeted as they are both a community need and are perceived as priority for intervention.

Vaccination Timing: There is evidence to suggest inadequacy of vaccination programs which provide doses at 2, 4, and 6 months, 4 years and in adolescence. There may be a role for earlier vaccination, in order to protect those under 6 months of age. Furthermore, there

may also be a role for the inclusion of those over the age of 20 in the national immunisation programme, as well as health care and childcare workers. Moreover, investment in screening, surveillance and patient education should be recommended.

Resource allocation: There is a need to mobilise resources. There may be a role for lobbying national and state governments to devote a greater proportion of the national budget to health care and disease prevention. Furthermore, there may be a role for the private sector (e.g. pharmaceutical companies) to also invest further in this disease in the form of vaccines, treatments, educational materials and awareness strategies. Human resources must also match financial resources, with appropriate medical staff providing increased vaccination and health promotion on this issue. Finally, building sustainable relationships between different bodies is key to the long-term success of health promotion, e.g. between Medicare Australia, the Australian Medical Association, public hospitals, pharmaceutical companies, state and federal health ministries.

Programme Implementation

Establishing an evidence base: This could be done by randomised controlled trial of vaccinating infants at the onset of labour, and another booster shot before the current regimen at 2 months to assess clinical outcomes. A randomised trial could also be done for adults over 20 years in limited geographical areas to assess efficacy, human resources and costs. A trial of up-skilling healthcare workers to be competent for routine pertussis screening in hospitals may be implemented and tried. Additionally, production of pamphlets and utilising media to promote

Table 2. A continuum of prevention activities for *Bordetella pertussis*: primordial, primary, secondary and tertiary prevention. * Indicates the author's suggestion.

Type of prevention	Examples
Primordial Prevention	<ul style="list-style-type: none"> - Government initiative to increase the availability of housing to decrease over-crowding. - Provision of adequate septic system to reduce chance of transmission of disease*. - Transport providing access to healthy food, educational institutions, health care and areas providing employment*. - Exclusion of infected children from school or day care until they have completed 5 days of effective antimicrobial therapy or full recovery. This should also include healthcare and childcare workers. [16] - Government-run public health promotion campaign to promote education and awareness about <i>Bordetella pertussis</i> infection*.
Primary Prevention	<ul style="list-style-type: none"> - Compulsory National Immunisation Program for high risk category Australians: 2, 4, 6 months, 4 years age and booster shot during adolescence. [1] - Access to prophylactic antibiotics for all household members, childcare attendees and healthcare persons regardless of immunisation status. [3] - Booster vaccination for preschool children*. - Cocoon Strategy: Vaccination for those planning pregnancy, or for both parents and other households after the birth of an infant (preferably prior to leaving hospital). [1,17] - Vaccination for adults working with young children, especially childcare and healthcare workers e.g. general practitioners (GPs). [1] - Vaccination of infants earlier than 6-8 weeks old. There is some evidence to suggest that a birth dose of pertussis vaccine, followed by doses at ages 3, 5 and 11 months resulted in earlier antibody responses compared with the standard Italian schedule for vaccination at 3, 5 and 11 months. [3] - Wearing facial masks during endemic seasons*. - Standard precautions, as well as droplet precautions (mask within three feet) recommended for children with pertussis interacting with non-pertussis children admitted to hospital. [16] - Surveillance of hygiene standards (hand washing and stethoscope cleaning) in the hospital environment to limit the spread of infection. Stethoscopes have long been identified as potential vectors of infection. [18] - Australia should maintain its involvement with the Global Pertussis Initiative (GPI), a global collaboration which provides evidence-based immunisation strategies. [3]
Secondary Prevention	<ul style="list-style-type: none"> - Antimicrobial agents: Erythromycin has been the gold standard for pertussis treatment for many years, however, new macrolides, such as clarithromycin and azithromycin are recommended by a recent Cochrane review and are equally effective as erythromycin with the added benefit of reduced side effects than erythromycin and better compliance. [3,6] - Notification to the health department or public health unit. [6] - Early determination of whether the patient is within the window period to receive treatment. [6] - Providing free routine screening: Particularly for high risk age categories such as less than 6 months (during compulsory infant checkups), adolescence (compulsory in schools) and 20 years and over and elderly (at every GP visit). Suggested screening techniques include the measurement of respiratory function, sputum analysis, blood culture, Polymerase Chain Reaction (PCR) and <i>Bordetella pertussis</i> serology*.
Tertiary Prevention	<ul style="list-style-type: none"> - Antimicrobial agents*. - Continued monitoring of respiratory rate, heart rate, oxygen saturation and lung function tests for potential complications*. - Bronchodilators*.

health awareness of pertussis could be trialled to assess coverage, efficacy, cost and human resources.

Health promotion actions: Traditionally, health promotion activities have focused on public information, education or communication as the main method for improving knowledge and changing behaviours and thus, this should be emphasised in a pertussis preventative strategy. Dissemination of information through mass media by advertising, radio, posters and pamphlets around healthcare centres could be implemented in a cost effective way.

Organisations could also work together with pharmaceutical companies supplying vaccination. Furthermore, identified cases of pertussis should be reported early to a public health authority by private and public hospitals. Finally, prior to registration of doctors with the medical board, they could be required to undergo pertussis training.

Monitoring and recording of programme implementation and quality control

Increased attention must be given to the development of performance indicators which can be used to assist in assessing good management of people and resources, and assessment of success or failure. [19] Cost-benefit analysis may be assessed for each class of preventative strategy, the availability of staff for an increasingly elderly population, assessment of penetration and impact of mass media and pamphlets for patient education could be accounted by production of surveys, and public notifications, mortality and morbidity data may constantly be monitored to assess efficacy of increased DTPa.

Program evaluation

Health literacy may be evaluated using measures such as assessing pertussis-related knowledge, attitudes, motivation, behavioural intentions, personal skills and self efficacy of the public. [19] Outcomes regarding internal governmental policy developmental process, and lobbying leading to legislative change could be reviewed using measures such as policy statements, resource allocation and

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organisational practices. Finally, data of social outcomes (such as quality of life, equity) and health outcomes (national data on reduced morbidity, disability, avoidable mortality) may be evaluated to assess whether the preventative strategy was successful, or, if there are any program failures, may be traced to re-examine potential solutions.

Conclusion

Despite the largely successful history of immunisation in dramatically decreasing the incidence of pertussis, especially in terms of the number of hospitalisations and deaths, a number of changes to the immunisation strategy may be overdue. Control of the disease still remains a challenge in 21st century Australia, with increased notification rates documented in those under the age of 6 months and over the age of 20. GPs, often the first point of contact, should familiarise themselves with the epidemiology those at greatest risk of pertussis, and offer vaccination accordingly. Moreover, individuals, health professionals, health organisations and governments must work synergistically to develop novel preventative strategies against modifiable risk factors, such as by increasing the number of booster vaccines, increasing surveillance, and greater dissemination of information to the population, to minimise burden of the disease for a sustainable future.

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Conflicts of interest

None Declared.

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The influence of vitamin D on cardiovascular disease

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Background: Vitamin D is essential for many biological functions in the body. Populations that are deficient in vitamin D have increased cardiovascular morbidity and mortality. Current research is controversial, and the evidence base is still developing. This review looks at the interaction between vitamin D levels and cardiovascular disease, including the major cardiovascular risk factors - diabetes, obesity, hyperlipidaemia and hypertension. **Methods:** A literature review was undertaken through MEDLINE / PubMed / Ovid / Springerlink / Web of Science databases. The terms, "vitamin D", "vitamin D deficiency", "cardiovascular risk", "cardiovascular disease", "structure", "function", "ergocalciferol", "cholecalciferol", "calcitriol", "vitamin D receptors", "1 α -hydroxylase", "diabetes", "obesity", "hypercholesterolaemia", "hyperlipidaemia" and "hypertension" were used. Sixty-eight articles were selected and analysed, with preference given to studies published in English and published within recent years. **Results:** There is a correlation between adequate vitamin D levels and type two diabetes mellitus, but limited research to support this. Obesity, physical inactivity and elevated circulating lipids are more common in vitamin D deficiency. These relationships have not been shown to be causal. Some studies have shown an inverse correlation between hypertension and vitamin D levels, while others have shown no relationship. **Conclusion:** The studies analysed show there is limited evidence to suggest that cardiovascular disease may be prevented by adequate vitamin D levels. There are few well-designed studies that demonstrate the relationship between the cardiovascular risk factors - diabetes, obesity, hyperlipidaemia, hypertension, and vitamin D. Further research is needed to clarify the influence of vitamin D on cardiovascular disease.



active 1,25-dihydroxyvitamin D₃ (calcitriol) under the influence of renal 1 α -hydroxylase predominantly in the kidney. [5,6]

1 α -hydroxylase is under the control of parathyroid hormone (PTH). Calcitriol is regulated by negative feedback on itself, by increasing production of 25-hydroxyvitamin D-24 hydroxylase. This enzyme catabolises calcitriol to its biologically inactive form, calcitric acid, which is excreted in the bile and urine. Other factors such as serum phosphorus, calcium and fibroblast growth factor 23 (FGF-23) can increase or decrease production of calcitriol. Increased serum calcium levels reduce PTH, causing down-regulation of 1 α -hydroxylase, reducing calcitriol, and therefore calcium levels. [5,6] A simplified diagram of the biological function of vitamin D is outlined in Figure 1.

1 α -hydroxylase is the rate-limiting step in production of calcitriol. Although calcidiol is the most abundant form of vitamin D in the blood, it has minimal capacity to bind to vitamin D receptors (VDRs). 1 α -hydroxylation of calcidiol to calcitriol causes vitamin D to gain affinity for VDRs. [7] In recent years, 1 α -hydroxylase has been found to exist at many extra-renal sites. The role of extra-renal vitamin D activation remains controversial, but may play a role in the hypothesised actions of vitamin D. [8]

VDRs are found in almost every cell in the body. Calcitriol actions occur through intracellular receptors and interaction with DNA via the classic steroid pathway. These receptors were originally thought to regulate genes responsible for regulation of serum calcium and phosphate. [1] More recently, they have been found to regulate transcription in many tissues and cells, including immune cells, bone marrow, skin, muscle and intestine. [1,9]

How does vitamin D affect cardiovascular disease?

Vitamin D deficiency has been associated with high blood pressure, risk for cardiovascular-related deaths, symptoms of depression, cognitive deficits and mortality. [10] Calcitriol inhibits renin synthesis, increases insulin production and increases myocardial contractility. [11-13] Vitamin D deficiency reduces serum calcium levels, causing an increase in PTH, which promotes atherosclerosis and cardiovascular risk. [14,15]

The majority of evidence for the role of vitamin D in cardiovascular disease (CVD) has arisen from studies involving patients with end stage renal disease. Cardiovascular mortality is ten to twenty times higher in

What is vitamin D, and how do you get it?

Vitamin D is a group of secosteroids, derived from steroid precursors by the opening of the steroid B-ring between carbons nine and ten. Vitamin D has a cis-triene structure which is susceptible to oxidation, ultraviolet (UV) light-induced conformational changes, heat-induced conformational changes and attack by free radicals. [1,2]

Cholecalciferol, also known as vitamin D₃, is a 27-carbon molecule derived from cholesterol. [2] It is available through diet and through synthesis in the skin. [1] 7-dehydrocholesterol found in skin is converted to previtamin D₃ following exposure to ultraviolet B (UVB) light. Previtamin D₃ is unstable and breaks down to vitamin D₃. This binds to vitamin D binding protein (VDBP) and is delivered to the liver and other sites of action via the circulatory system. [3,4] Vitamin D levels are regulated in the body in a number of ways. While exposure to UVB radiation causes vitamin D₃ production in the skin, excessive exposure to sunlight degrades it into inactive photoproducts. [5]

Ergocalciferol, also known as vitamin D₂, is a 28-carbon molecule produced by irradiation of ergosterol found in plant and fungi, which is available through diet. [2,4] Vitamin D₂ and D₃ (available via diet) are absorbed with fat in the gastrointestinal system into chylomicrons, which are delivered to the liver or storage sites outside the liver, such as adipose tissue. [1]

The liver converts vitamin D₃ to biologically inactive 25-hydroxyvitamin D₃ (calcidiol). This is converted to biologically

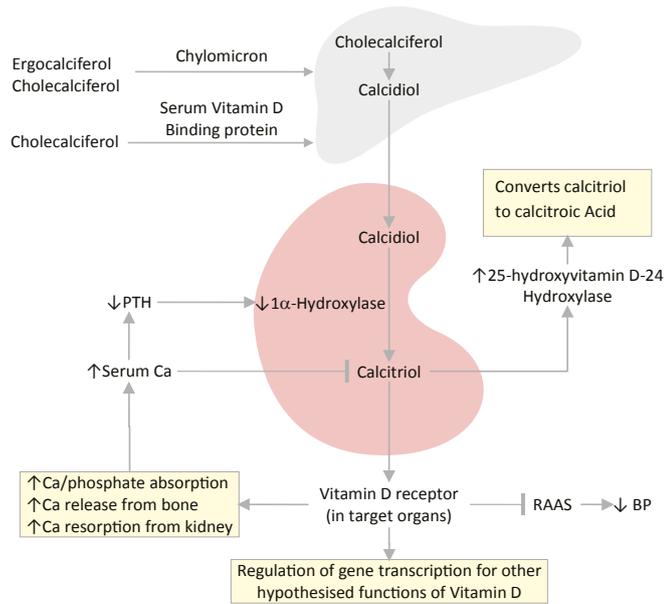


Figure 1. The biological function of vitamin D. Extra-renal sites of 1 α -hydroxylation are not shown in this diagram.

patients undergoing dialysis. [16] In patients using dialysis, the risk of death from CVD can be reduced with vitamin D replacement. [17,18]

As kidney function deteriorates, calcitriol levels decline. [19] Reduced calcitriol production can lead to hypocalcemia, and in turn, compensatory elevated PTH. Overstimulation of the parathyroid gland eventually leads to secondary hyperparathyroidism (SHPT). [20] Patients with ESRD are thought to suffer from reduced cardiac inotropy, increased heart weight, increased myocardial collagen content, and increased vascular smooth muscle cell proliferation as a result of the vitamin D depletion. PTH excess may impair intracellular calcium metabolism of the cardiomyocyte and promotes chronic atherosclerosis. Elevated PTH may increase cardiac contractility, insulin resistance, calcium and phosphate deposition in vessel walls, chronic myocardial calcification, and chronic heart valve calcification. [14,15] In patients with SHPT, treatment advice usually consists of correction of calcitriol deficiency using calcitriol or vitamin D analogues. [6]

Mechanisms for cardiovascular risk reduction with vitamin D supplementation include the inhibition of smooth muscle proliferation, the suppression of vascular calcification, the down-regulation of inflammatory cytokines, the up-regulation of anti-inflammatory cytokines, and the negative regulation of the renin-angiotensin-aldosterone system (RAAS). [21-26] Inappropriate stimulation of the RAAS is associated with hypertension, myocardial infarction and stroke. [14] Calcitriol treatment has been shown to reduce blood pressure, renin activity and angiotensin II levels. [27] The effects of vitamin D deficiency on the cardiovascular system are outlined in Figure 2.

A systematic review and meta-analysis looked at the relationship between the naturally occurring level of vitamin D and cardiometabolic disorders including CVD, diabetes and metabolic syndrome. [28] Twenty-eight studies were selected, including nineteen cross-sectional studies, three case-control studies and six cohort studies, analysing 99,745 patients. [28] High vitamin D levels were associated with a 43% reduction in cardiometabolic disorders. [28] There was a significant association between high levels of vitamin D and risk of having cardiovascular disease (33% reduction), type two diabetes (55% reduction) and metabolic syndrome (51% reduction). [28] Vitamin D supplementation has been shown to have a protective effect in limited studies of CVD, but further research is needed. [29]

Diabetes

The research surrounding the interaction between vitamin D supplementation and type two diabetes mellitus is controversial. To

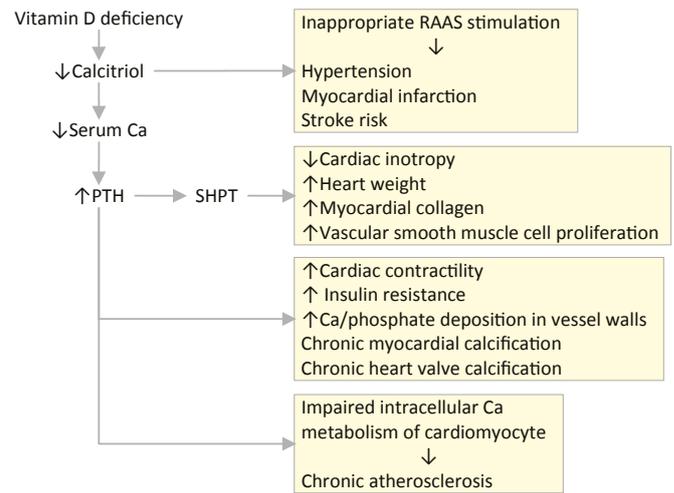


Figure 2. The role of vitamin D deficiency in cardiovascular disease.

date, there have been no adequate, large and prospective, randomised controlled trials to test the efficacy of vitamin D supplementation for the prevention and treatment of type two diabetes mellitus. The current available data allows a recommendation that further research be conducted to determine whether adequate vitamin D levels may prevent the onset of type two diabetes. Type one diabetes mellitus will not be discussed in this review.

Insulin resistance has been associated with low serum vitamin D, which improved after treatment with vitamin D. [30-36] One study demonstrated a positive relationship between calcitriol and insulin sensitivity, and a negative effect of vitamin D deficiency on beta cell function. [12] These studies are limited by small sample size, subject selection and lack of randomisation. However, there was a clinical correlation and it is worthwhile investigating further the possibility of improvement in insulin sensitivity with vitamin D supplementation. Serum blood sugar levels and prevalence of type two diabetes mellitus increases with age, and vitamin D levels tend to fall with age. [37,38] Type two diabetes is associated with systemic inflammation, which may induce beta-cell dysfunction and death. [39] Several studies show that vitamin D could directly affect beta-cell growth and differentiation via modulation of systemic inflammation and the immune response. [39-42] One of these was a double-blinded 39-week follow-up study of interleukin-1 blockade with anakinra. [40] Although being limited by small sample size and limitations in subject selection, the study showed improvement in markers of systemic inflammation 39 weeks after treatment withdrawal. [40]

Several studies indicate that calcitriol regulates beta-cell function by regulating intracellular calcium levels. This is thought to influence insulin secretion, increase beta-cell resistance to apoptosis and increase beta-cell replication. Calcitriol is thought to bind to nuclear VDRs in the beta-cell to increase preproinsulin mRNA level. Research to support this hypothesis is limited, due to being conducted in rats. [39,43-45]

Obesity and hyperlipidaemia

Studies have shown that high body mass index (BMI) is associated with low serum vitamin D levels. [46] Vitamin D is fat soluble and readily stored in adipose tissue. [1,47] Sequestration of cholecalciferol in adipose tissue reduces bioavailability in obese individuals. [1,48,49] The distribution of fat may be associated with vitamin D status, but this relationship may be dependent on metabolic factors. [49]

Vigorous physical activity is a strong and modifiable contributor to vitamin D status. This may be due to sun exposure correlated with physical activity, however, a number of studies have shown the positive effect on vitamin D status may be independent of sun exposure. [50-54] Further research is needed to clarify this.

A large, prospective study of the modifiable predictors of vitamin D

status was conducted using 2,621 healthy individuals aged 55-74 in the USA. [46] Predictors of low vitamin D status were found to be low dietary vitamin D intake, BMI > 30kg/m², physical inactivity and low milk and calcium supplement intake. [46] There is an inverse relationship between apolipoprotein A-I and high density lipoprotein cholesterol with vitamin D levels in a survey of 358 Belgian people. [55] This relationship was not shown to be causal, but further research is warranted to see if vitamin D provides this cardioprotective link.

Vitamin D deficiency may increase insulin resistance and thereby increase circulating lipids, but supplementation has not been shown to improve circulating lipid levels. [56,57] Statin therapy increases the circulating levels of 7-dehydrocholesterol, leading to an increase in conversion to vitamin D (in the presence of UVB radiation), and therefore vitamin D levels. [58-61]

Hypertension

To date, there are few good quality randomised controlled trials looking at the relationship between vitamin D levels and blood pressure. There is weak evidence to suggest that there may be a relationship between the two, however, further research is needed to draw any conclusions that may change the management of blood pressure.

Vitamin D may regulate blood pressure via an interaction with the RAAS, which is often activated in hypertension. Calcitriol is a known negative regulator of the RAAS. [11,21] The effects of vitamin D on the suppression of renin activity may be due to increased intracellular calcium levels. [62] It is hypothesised that vitamin D regulation of renin is independent of calcium metabolism, by regulating renin mRNA production with VDRs. [11] This study was completed using a line of cells derived from transgenic mice kidney tumours. [11]

There are some studies which show an inverse correlation between vitamin D levels and blood pressure. [63-66] A meta-analysis which included eleven randomised controlled trials (small, variable methodological quality) found weak evidence to support a small effect of vitamin D on blood pressure in studies of hypertensive patients. [67] There was a small statistically significant reduction in diastolic blood pressure, and no significant reduction in systolic blood pressure in hypertensive subjects supplemented with vitamin D or UV radiation. [67]

Several studies have shown differing results when trying to establish a relationship between vitamin D intake and hypertension. [10] There

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are two cross-sectional studies that have been completed using the Third National Health and Nutrition Examination Survey data. One study demonstrated a significant difference in systolic blood pressure and pulse pressure between the highest and lowest quintile groups divided by vitamin D level. [10,63] Participants with hypertension were excluded from analysis. [63] Another study revealed increased systolic blood pressure with reducing levels of vitamin D, and a twenty percent reduction in systolic blood pressure in those with vitamin D levels greater than 80 nmol/L compared with those with less than 50 nmol/L. [64] Both of these studies had a good sample size, but were limited by the methods of the study. [10] A cross-sectional study using a different data set with low prevalence of vitamin D deficiency showed no association between systolic blood pressure and vitamin D level. [10,65] A different study did not show any significant relationship between vitamin D levels and blood pressure after adjusting for confounding variables, however, this may have been due to low estimated vitamin D intake. [10,68]

Conclusion

Vitamin D is an important molecule to consider in the pathogenesis of cardiovascular disease. Current research shows that vitamin D deficiency contributes to cardiovascular morbidity and mortality. The mechanisms proposed for this include direct actions on the heart and vasculature, as well as by increasing the risk of cardiovascular risk factors such as diabetes, obesity, hyperlipidaemia and hypertension. Further research is needed to clarify the influence of vitamin D on cardiovascular disease and its risk factors, and whether vitamin D is an efficient, cost-effective and safe intervention to prevent cardiovascular morbidity and mortality.

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Conflicts of interest

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Is cancer a death sentence for Indigenous Australians? The impact of culture on cancer outcomes

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Aim: Indigenous Australian cancer patients have poorer outcomes than non-Indigenous cancer patients after adjusting for age, stage at diagnosis and cancer type. This is not exclusive to the Indigenous population of Australia. The aim of this review is to explore the reasons why Indigenous Australians face a higher cancer mortality rate when compared to their non-Indigenous counterparts.

Methods: A literature search was conducted using PubMed and Medline to identify articles with quantitative research on the differing survival rates and cancer epidemiology, and qualitative data on postulated reasons for this discrepancy. Qualitative studies, non-systematic topic reviews, quality improvement projects and opinion pieces were also reviewed in this process, with the belief that they may hold key sources of Indigenous perspectives, but are undervalued in the scientific literature. **Results:** Although all-cause cancer incidence is lower within Indigenous Australians, the probability of death was approximately 1.9 times higher than in non-Indigenous patients. Occurrence of cancer types differ slightly among the Indigenous population, with a higher incidence of smoking-related cancers such as oropharyngeal and lung cancers, and cancer amenable to screening such as cervical cancer. Indigenous patients generally have a later stage at diagnosis, and are less likely to receive curative treatment. This discrepancy has been attributed to health service delivery issues, low uptake of screening, preventative behaviours, communication barriers, socioeconomic status and non-biomedical beliefs about cancer.

Conclusion: The implication of these findings on the future of Indigenous cancer care indicates the fundamental social, cultural and serviced-based change required for long-term sustainable improvement in reducing Indigenous mortality rates. To 'close the gap' we need to make further collaborative system changes based on Indigenous cultural preferences.



reasons for this discrepancy. Qualitative studies, non-systematic topic reviews, quality improvement projects and opinion pieces were also reviewed in this process, with the belief that they may hold key sources of Indigenous perspectives, but are undervalued in the scientific literature. Combinations of key words such as 'Indigenous', 'cancer', 'incidence', 'mortality', 'non-Indigenous', and 'cultural beliefs' were used, in addition to criteria limiting articles to those published after 2000 and within Australia, although some key international references were included.

Generally, Indigenous Australians have a life expectancy seventeen years younger than their non-Indigenous counterparts, and a burden of chronic disease 2.5 times higher. [5] This is not exclusive to the Indigenous population of Australia; similar findings have been shown for Indigenous people of Canada, New Zealand and the United States. [6,7,8] The Aboriginal and Torres Strait Islander people of Australia, who account for 2.4% of the total population, will be referred to as Indigenous people for the purpose of this review, [9] although their separate cultural entities are recognised.

Introduction

Indigenous Australian cancer patients have much poorer outcomes than non-Indigenous cancer patients after adjusting for age, stage at diagnosis and cancer type. [1] Statistics from 2005 show that cancer was the third highest cause of death in Indigenous people, as for all Australians, causing 17% and 30% of all deaths respectively. [1,3] However after adjusting for age and sex, Indigenous people had a 50% higher cancer death rate. [4] Indigenous Australians have a higher incidence of rapidly-fatal cancers that are amenable to screening or are preventable, particularly lung and other smoking related cancers. [2] One of the major contributors to increased mortality is the advanced stage at cancer diagnosis. In addition to this, Indigenous people are less likely to receive adequate treatment. The aim of this review is to explore the reasons why Indigenous Australians face a higher cancer mortality rate when compared to their non-Indigenous counterparts. This review will display the epidemiology of cancer types and discuss the grounds for this discrepancy, including a focus on the causes for advanced stage at diagnosis, geographical distribution of the population, socioeconomic status, service delivery and cultural beliefs about cancer.

A literature search was conducted using PubMed and Medline to identify articles with quantitative research on the differing survival rates and cancer epidemiology, and qualitative data on postulated

Epidemiology

Indigenous people in the Northern Territory diagnosed with cancer between 1991 and 2000 were 1.9 times more likely to die than other Australians, after adjusting for cancer site, age and sex (Figure 1). [10] The prevalence of cancer types differed among the Indigenous population, with a higher incidence of, and mortality from, smoking-related cancers such as oropharyngeal and lung cancers, and cancers amenable to screening, such as cervical and bowel cancer. [10,11] In addition, studies from New South Wales, the Northern Territory and Queensland have found that Indigenous people are more likely to have advanced disease at diagnosis for all cancers combined. [2,12,13] Notably, lung cancer is diagnosed earlier in Indigenous people; this is thought to be due to the high prevalence of lung conditions such as tuberculosis and chronic lung disease among the Indigenous population. [2] Statistics show that only 11% of Indigenous bowel cancer patients in the Northern Territory, compared to 32% of non-Indigenous patients, had an early diagnosis. This has potential for improvement through the use of faecal occult blood programs as a cost effective screening tool. [6] In addition to the late stage at diagnosis, the low rate of cancer survival in Indigenous patients can be, in part, attributed to the prevalence of high fatality cancers, treatment-limiting comorbidities and high uptake of palliative or non-aggressive treatment options. [2]

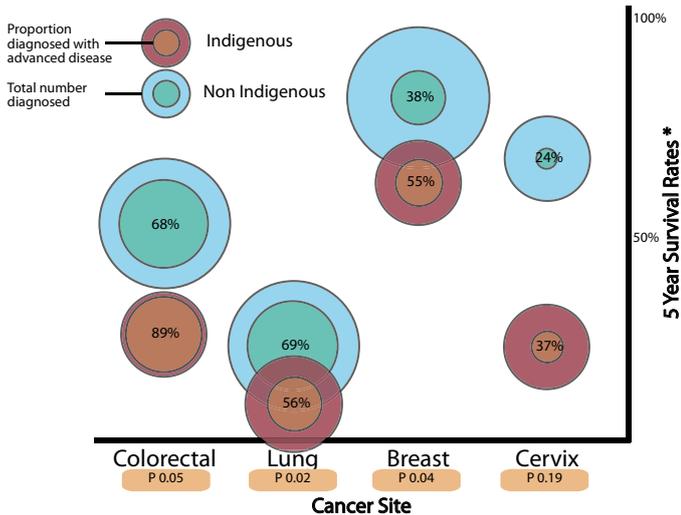


Figure 1. Incidence of cancer by site and five year survival in the Northern Territory, Australia, between 1991-2000. [2]

Studies from across a number of states in Australia have shown that Indigenous patients are less likely to undergo treatment. In a study reported by Hall *et al.* in Western Australia, 26 (9.5%) of 274 Indigenous lung cancer patients underwent surgery, as compared to 1693 (12.9%) of 13,103 non-Indigenous lung cancer patients, from 1982 to 2001. [16] In the same time period, one (1.5%) of 64 Indigenous prostate cancer patients, versus 1,787 (12.7%) of 12,123 non-Indigenous prostate cancer patients underwent surgery. The study concluded that the Indigenous population with prostate or lung cancer were less likely to undergo surgery than their non-Indigenous counterparts. [14] A Queensland study by Valery *et al.* also reported that Indigenous cancer patients were less likely to undergo surgical treatment. [9] This may partly be explained by advanced stage at diagnosis; however, the results are statistically significant, demonstrating under-treatment after this adjustment. Treatment choice and barriers to care were identified as important contributors to this discrepancy. [14]

Longitudinal trends from 1995 to 2005 in the Northern Territory reported a downward trend in all cancer incidence among the non-Indigenous people, as opposed to an increase in Indigenous people. The all-cancer mortality declined significantly within non-Indigenous people, while there was little change in the death rate of Indigenous people. [10] Nation-wide trends between 1982 and 2007 show that the incidence of all cancers combined increased from 383 cases per 100,000 to 485 per 100,000. [15]

Rural and Remote Locations

Lower survival rates were observed in Queensland, Western Australia and the Northern Territory in Indigenous cancer patients from remote communities. [4,16] Indigenous people are ten times more likely to live in remote areas of Australia than non-Indigenous people. [17] This has implications for service delivery of screening, diagnosis and treatment, as well as access to preventative health education. In rural and remote Australia there is a shortage of healthcare providers and adequate primary health care facilities to cater for the vast geographical distances. There is a difficulty in ensuring transport links between major centres for patients requiring referral. These factors probably contribute to the outcomes.

Socioeconomic Status

Like other Indigenous populations, Indigenous Australians are overrepresented in the low socioeconomic strata. [1,2] Since the colonisation of Australia by the non-Indigenous population, the Indigenous people have progressively lost their cultural expression and practices, resulting in disempowerment. [8] Subsequent 'welfare dependency' with continuing loss of skills, unemployment and hopelessness have been suggested as contributory factors. [12] There are a multitude of reasons as to why disempowerment has manifest

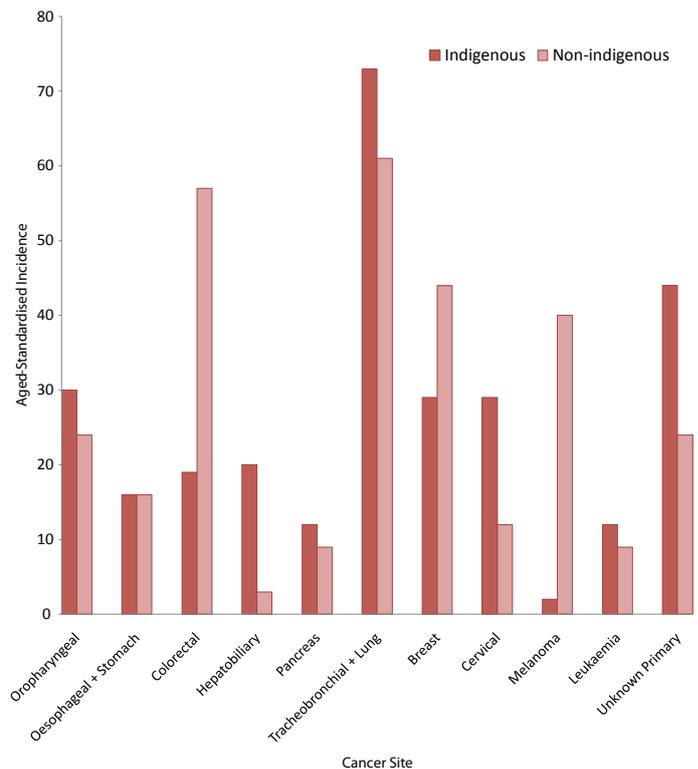


Figure 2. Incidence of Indigenous and Non-Indigenous Cancer Patients in the Northern Territory, Australia, between 1991-2005. [10]

in poor levels of education, employment and health outcomes, which is beyond the scope of this discussion. In addition, Indigenous Australians are more likely, in varying degrees, to be exposed to poor environmental health such as disadvantaged living conditions. This includes overcrowding, poor nutrition and obesity, tobacco, excessive alcohol consumption and other drugs, and higher rates of human papillomavirus (HPV) infection, which are linked to the aetiology of cervical and head and neck cancers. [1,11,17] Behavioural risk factors linked to low socioeconomic status may contribute to higher levels of comorbidities.

Culture

Cultural isolation, power imbalances and differing health beliefs of cancer causation are patient factors that also contribute to poorer prognosis. Indigenous people are sensitive to power imbalances in their interaction with healthcare providers. [12] Psychological stress, common to many vulnerable populations, has been consistently associated with sub-optimal health outcomes for Indigenous people and an important obstacle in accessing healthcare. Peiris *et al.* believes that 'cultural safety' within healthcare facilities is paramount in addressing this problem. [12] Creating open-door policies, welcoming waiting rooms and reception staff who know the community are means of reorientating the health services and preventing the cultural disconnect. [12] However, there is a lack of community-controlled health services in many areas, and a relative lack of skilled Indigenous people in the workforce. Improving these factors would greatly enhance the cultural safety and community-specific delivery of health. [4,12] Studies comparing the Maori and Pacific Islander people in New Zealand have extrapolated on similar causes of ethnic inequalities in access to culturally acceptable health services. [6,7,8]

Language

In 2002, 66% of Indigenous Australians in the Northern Territory reported speaking a language other than English at home; in Western Australia, South Australia and Queensland the number of Indigenous language speakers was eleven to fourteen percent. [18] A study by Condon *et al.* reported that cancer survival was strongly associated with the patient's first language. [2] After adjusting for treatment, cancer stage and site, it was shown that the risk of death for Indigenous

native language speakers was almost double that of Indigenous English speaking and non-Indigenous patients. [2] It is postulated that communication difficulties, social and cultural 'disconnect' from mainstream health services and poor health literacy may be linked to native first language. [9] This valuable finding reinforces the importance of using Aboriginal Health Workers and translators in clinical practice.

Beliefs about Cancer

Attitudes to cancer and medical services strongly influence the use of diagnostic or curative care. Shahid *et al.* interviewed Indigenous people from various geographical areas in Western Australia about their beliefs and attitudes towards cancer. [3] The findings were surprising. Many Indigenous people believe cancer is contagious, and attributed cancer to spiritual curses, bad spirits or as punishment from a past misdeed. It was found that blaming others or one's own wrongdoing as a cause of cancer or illness is widespread within Aboriginal communities, where spiritual beliefs about one's wellbeing predominate. [3] Shahid *et al.* claimed that attribution of cancer to spiritual origins lead to acceptance of disease without seeking healthcare. [3] In addition, the Indigenous cancer sufferer may feel ashamed of their 'wrongdoings' and hide their symptoms, delaying diagnosis. [3]

Fatalistic attitudes towards cancer diagnosis in the general Australian population has changed in recent times, with the dissemination of information regarding curative cancer treatments, and the shifting focus toward understanding the biological basis of cancer and educating the public about screening and preventative behaviours such as the bowel cancer screening and the HPV vaccination. However, the low socioeconomic status and poor educational background of many Indigenous Australians has limited their access to such information. [3] In many Indigenous communities the fatalistic expectations of a cancer diagnosis remain. Such fatalistic beliefs are associated with delays in cervical cancer screening, late presentation of cancer symptoms, and patients who are lost to follow-up, contributed to by the aforementioned beliefs. For example, some Indigenous women with cervical cancer in Queensland blamed cancer on the loss of a traditional lifestyle. [19] Other beliefs about cancer are that screening protects from cancer and that cancer is contagious. Studies from New Zealand, Canada and the US have shown similar themes concerning non-biomedical Indigenous beliefs about cancer. [6]

In addition to the view that "cancer means death" were views of overreliance or mistrust in doctors. Often personal stories of an individual's unmet expectations of the medical system spread within the community and influenced other's attitudes; examples include patients who had finished treatment, thought they had been cured

The poor outcomes of Indigenous cancer patients are multifactorial:

- Indigenous people are ten times more likely to live in rural and remote locations, making health service delivery difficult. [16]
- There are more than 100 Indigenous language variations throughout Australia. Communication barriers are identified as one of the most significant prognostic factors for cancer patients in Australia. [9,18]
- Traditional, non-biomedical beliefs about cancer causation are common among Indigenous communities, including contributing cancer to bad spirits, past misdeeds or the disease being contagious. [3,6,20]
- Indigenous people are more likely to have poorer health behaviours; 2.2 times more likely to be daily smokers, 1.2 times more likely to be overweight and 6.6 times more likely to have no daily vegetable intake. [1,2]
- There are cultural barriers in seeking 'Westernised' health care. Many vulnerable populations experience psychological stress and are sensitive to power imbalances within mainstream healthcare facilities. [3,18,19,21]

of cancer, and were then lost to follow-up, or the idea that screening prevents cancer. [20] Traditional healing still has a role in many Indigenous communities for health and wellbeing, as well as the importance during palliation of the cancer patients, often as a link to their connection with their country and ancestral roots. [3]

Recommendations

Culturally-appropriate service delivery

Diagnosing cancers earlier in the Indigenous population would increase the chance for curative treatment and reduction in overall mortality. Increasing primary health care services and their culturally appropriate delivery would address this need. However, improving the access to and use of relevant services for Indigenous people currently remains a challenge. For women's issues, there may be stigma, shame and embarrassment associated with sexually transmitted infections and cervical cancer, as well as the cultural factors associated with denial of symptoms and gender roles of healthcare workers. [20] Service delivery failures are related to inadequate or inappropriate recall-systems, privacy during screening, especially in small communities, sex of the healthcare provider, timing and location of screening, discontinuity of care, difficulty maintaining cold chain and promoting vaccinations such as Gardasil™. [17] National data for breast and cervical cancer screening reveals that Indigenous women participate at about two-thirds of the national rate. However, the implementation of the culturally acceptable "Well Women's Screening Program" in the Northern Territory, substantially improved Indigenous participation in PAP test screening from 33.9% in 1998 to 44% in 2000. [19] Similar initiatives have also been successfully implemented in Queensland. [22] This highlights the efficacy of culturally appropriate services tailored to the population.

Education

Programs to decrease tobacco use and to improve other behavioural risk factors need to be designed appropriately for use in the setting of communication difficulty and poor health literacy, and they need to address the cultural role of smoking in Indigenous people. [1] In addition, health service delivery improvements such as health education, promotion, screening programs and cultural safety, such as those demonstrated in the successful "Well Women's Screening Program", [19] will also contribute to a successful intervention.

Conclusion

Australian national 'Closing The Gap' targets include "to halve the life expectancy gap [between Indigenous and non-Indigenous Australians] within a generation." [5] Language, cultural barriers, geographical distance, low socioeconomic status, high-risk health behaviours and traditional and non-biomedical beliefs about cancer are all reasons why Indigenous Australians have worse cancer outcomes than non-Indigenous Australians. The implication of these findings on the future of Indigenous cancer care and on meeting the national targets signifies the fundamental social, cultural and service-based changes required for long-term sustainable improvement in reducing the Indigenous mortality rates. The underlying cultural beliefs and individual perceptions about cancer must be specifically addressed to develop effective screening and treatment approaches. Educational material must be designed to better engage Indigenous people. In addition, Aboriginal cancer support services and opportunities for Aboriginal cancer survivors to be advocates within their communities may increase Indigenous peoples' willingness to accept modern oncology treatments. Through these improvements, a tailored approach to Indigenous cancer patients can meet the spiritual, cultural and physical needs that are imperative for a holistic approach in their management.

Conflicts of interest

None declared.

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Control of seasonal influenza in healthcare settings: Mandatory annual influenza vaccination of healthcare workers

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Kathryn Franks is currently a fifth year medical student from James Cook University on rotation at the Mackay Base Hospital. She has a passion for public health and paediatric medicine, and is soon to commence a research project on social media and the provision of health care information during pregnancy. She hopes to train as a paediatric oncologist in the future.

Introduction: The aim of this review is to emphasise the burden and transmission of nosocomial seasonal influenza, discuss the influenza vaccine and the need for annual influenza vaccination of all healthcare workers, discuss common attitudes and misconceptions regarding the influenza vaccine among healthcare workers and means to overcome these issues, and highlight the need for mandatory annual influenza vaccination of healthcare workers. **Methods:** A literature review was carried out; Medline, PubMed and The Cochrane Collaboration were searched for primary studies, reviews and opinion pieces pertaining to influenza transmission, the influenza vaccine, and common attitudes and misconceptions. Key words used included “influenza”, “vaccine”, “mandatory”, “healthcare worker”, “transmission” and “prevention”. **Results:** Seasonal influenza is a serious disease that is associated with considerable morbidity and mortality and contributes an enormous economic burden to society. Healthcare workers may potentially act as vectors for nosocomial transmission of seasonal influenza. This risk to patients can be reduced by safe, effective annual influenza vaccination of healthcare workers and has been specifically shown to significantly reduce morbidity and mortality. However, traditional strategies to improve uptake consistently fail, with only 35 to 40% of healthcare workers vaccinated annually. Mandatory influenza vaccination programs with medical and religious exemptions have successfully increased annual influenza vaccination rates of healthcare workers to >98%. Exemption requests often reflect misconceptions about the vaccine and influenza, and reflect the importance of continuous education programs and the need for a better understanding of the reasons for compliance with influenza vaccination. **Conclusion:** Mandatory annual influenza vaccination of healthcare workers is ethically justified and, if implemented appropriately, will be acceptable. Traditional strategies to improve uptake are minimally effective, expensive and inadequate to protect patient safety. Therefore, low voluntary influenza vaccination rates of healthcare workers leave only one option to protect the public: mandatory annual influenza vaccination of healthcare workers.



Transmission of seasonal influenza

The influenza virus attaches and invades the epithelial cells of the upper respiratory tract. [8] Viral replication in these epithelial cells leads to pro-inflammatory cytokines, and necrosis of epithelial cells. [8] Influenza is primarily transmitted from person to person by droplets that are generated when an infected person breathes, coughs, sneezes and speaks. [8] These droplets settle on the mucosal surfaces of the upper respiratory tract of susceptible persons; thus transmission of influenza primarily occurs in those who are near the infected person. [8]

The influenza vaccine

The influenza vaccines currently available in Australia are inactivated, split virion or subunit vaccines, produced using viral strains propagated in fertilised hens' eggs. [9] The inactivated virus is incapable of replication inside the human body, and thus incapable of causing infection. [10] Influenza vaccines are trivalent, i.e. they protect against three different strains of influenza. [9] As influenza viruses are continually subject to antigenic change, annual adaptation of the influenza vaccine is needed to ensure the vaccine provides protection against the virus strains likely to be circulating during the influenza season. [9] The composition of the influenza vaccine in 2011 covered pandemic H1N1 2009 (swine flu), H3N2 and B strains of influenza. [11] Influenza vaccines are included in the Australian National Immunisation Program only after evaluation of their quality, safety, effectiveness and cost-effectiveness for its intended use in the Australian population. [9] The only common adverse effect of the influenza vaccine is minor injection site soreness for one to two days. [10] Influenza vaccine effectiveness depends on the age and immune status of the individual being vaccinated, and on the match between the strains included in the vaccine and those strains circulating in the community. [12] The influenza vaccine is 70 to 90% effective in preventing influenza infection in healthy individuals under 65 years of age; the majority of healthcare workers fall into this category. [12] Influenza vaccination has been shown to be 88% effective in preventing laboratory-confirmed influenza in healthcare workers. [13]

The need for annual influenza vaccination

Transmission of influenza has been reported in a variety of healthcare settings and healthcare workers may often be implicated in the outbreaks. [13] Healthcare workers are at an increased risk of acquiring seasonal influenza because of exposure to the virus in both

Introduction

Each year, between 1,500 and 3,500 Australians die from seasonal influenza and its complications. [1] The World Health Organization (WHO) estimates that seasonal influenza affects five to fifteen per cent of the population worldwide annually, with an associated three to five million cases of serious illness and 250,000-500,000 deaths. [2] In Australia, it is estimated that seasonal influenza causes 18,000 hospitalisations and over 300,000 general practitioner (GP) consultations every year. [3] Nosocomial seasonal influenza is associated with considerable morbidity and mortality among the elderly, neonates, immuno-compromised and patients with chronic diseases. [4] The most effective way to reduce or prevent nosocomial transmission of seasonal influenza is annual influenza vaccination of all healthcare workers. [5,6] The Centre for Disease Control and Prevention (CDC) has recommended annual influenza vaccination of all healthcare workers since 1981, and the provision and administration of the vaccine to healthcare workers at the work site, free of charge, since 1993. [7] Despite this, only 35% to 40% of healthcare workers are vaccinated annually. [8]

the healthcare and community settings. [13] However, simply staying home from work during symptomatic illness is not an effective strategy to prevent nosocomial transmission of seasonal influenza. [10] The incubation period ranges from one to four days; the contagious period begins before symptoms appear, and the virus may be shed for at least one day prior to symptomatic illness. [4,10] Less than 50% of people show classic signs of influenza; asymptomatic healthcare workers may fail to recognise that they are infected, yet can shed the virus for five to ten days. [13,14] Symptomatic healthcare workers also often continue to work despite the presence of symptoms of influenza. [10,15] In one study, 23% of serum samples from healthcare workers contained specific antibody suggesting seasonal influenza infection during a single season; however, 59% of those infected could not recall influenza-like illness and 28% were asymptomatic. [13] The direct implication of this fact is that healthcare workers themselves may potentially act as vectors for nosocomial transmission of seasonal influenza to patients who are at increased risk of morbidity and mortality from seasonal influenza. [10] Many of these patients do not mount an appropriate immune response to influenza vaccination, making vaccination of healthcare workers especially important. [16] Only 50% of residents in long-term care settings develop protective influenza vaccination-induced antibody titres. [17]

Influenza vaccination of healthcare workers may reduce the risk of seasonal influenza outbreaks in all types of health care settings and has been specifically shown to significantly reduce morbidity and mortality. [12] A randomised controlled trial evaluating the effect of annual influenza vaccination of healthcare workers found that it was significantly associated with a 43% reduction in influenza-like illness and a 44% reduction in mortality among geriatric patients in long-term care settings. [12] Furthermore, an algorithm evaluating the effect of annual influenza vaccination of healthcare workers on patient outcomes predicted that if all healthcare workers in healthcare settings were vaccinated annually with the influenza vaccine, then approximately 60% of patient influenza infections could be prevented. [18]

Although a number of factors contribute to the overall burden of seasonal influenza, the economic burden to society results primarily from the loss of working time/productivity associated with influenza-related work absence and increased use of medical resources required to treat patients with influenza and its complications. [19] Typically, the indirect costs associated with loss of working time/productivity due to illness account for the greater proportion (>80%) of the economic burden of seasonal influenza. [19] One study reported those healthcare workers who received the influenza vaccine had 25% fewer episodes of respiratory illness, 43% fewer days of sickness absenteeism due to respiratory illness and 44% fewer visits to physicians' offices for upper respiratory illness than those who received placebo. In a review of studies that confirmed seasonal influenza infection using laboratory evidence, the mean reported sickness absenteeism per episode of seasonal influenza ranged from 2.8 to 4.9 days for adults. [19] Furthermore, a retrospective cohort study investigating the association between influenza vaccination of emergency department healthcare workers and sickness absenteeism found that a significantly larger proportion took sick leave because of influenza-like illness in the vaccine non-recipient group (55% against 30.3%). [20]

Attitudes and misconceptions

Self-protection, rather than protection of patients, is often the dominant motivation for influenza vaccination. Many healthcare workers report they would be more willing to be vaccinated against pandemic influenza, which is perceived to be more dangerous than seasonal influenza. [15] One study found that the most popular reason (100% of those surveyed) for receiving the influenza vaccine among healthcare workers was self-protection against influenza. [21] Seventy percent of healthcare workers were also concerned about their colleagues, patients and community in preventing cross-infection. [21]

Popular reasons mentioned for not receiving the influenza vaccine included "trust in, or the wish to challenge natural immunity", "physician's advice against the vaccine for medical reasons", "severe localised effects from the vaccine" and "not believing the vaccine to have any benefit." [21] A multivariate analysis of a separate study revealed that "older age", "believing that most colleagues had been vaccinated" and "having cared for patients suffering from severe influenza" were significantly associated with compliance with influenza vaccination, with the main motivation being "individual protection". [22] Lack of information as to effectiveness, recommended use, adverse effects of the vaccine and composition, again reflect the importance of continuous education programs and the need for a better understanding of the reasons for compliance with influenza vaccination. [22]

Major issues

Analysis of interviews with healthcare workers indicated that successfully adding mandatory annual influenza vaccination to the current policy directive would require four major issues to be addressed: providing and communicating a solid evidence base supporting the policy directive; addressing the concerns of staff about the influenza vaccine; ensuring staff understand the need to protect patients; and addressing the logistical challenges of enforcing an annual vaccination campaign. [23] A systematic review of influenza vaccination campaigns for healthcare workers revealed that a combination of education or promotion and improved access to the influenza vaccine yielded greater increases in coverage among healthcare workers. [24] Campaigns involving legislative or regulatory components such as mandatory declination forms achieved higher rates than other interventions. [24]

Influenza vaccination is currently viewed as a public health initiative focused on personal choice of employees. [12] However, a shift in the focus of vaccination strategy is appropriate – seasonal influenza vaccination of healthcare workers is a patient health and safety initiative. [12] In 2007, the CDC Advisory Committee on Immunisation added a recommendation that health care settings implement policies to encourage influenza vaccination of healthcare workers with informed declination. [25] A switch from influenza vaccination of healthcare workers on a voluntary basis to a mandatory policy should be considered by all public-health bodies. [4]

Mandatory annual influenza vaccination

Fifteen states in the USA now have laws requiring annual influenza vaccination of healthcare workers, although they permit informed declination; and at least five states require it of all healthcare workers. Many individual medical centres have instituted policies requiring influenza vaccination, with excellent results. [26]

A year-long study of approximately 26,000 employees at BJC HealthCare found that a mandatory influenza vaccination program successfully increased vaccination rates to >98%. [27] Influenza vaccination was made a condition of employment for all healthcare workers, with those still not vaccinated or exempted, terminated after one year. [27] Medical or religious exemption could be sought, including hypersensitivity to eggs, prior hypersensitivity reaction to influenza vaccine, and history of Guillain-Barre syndrome. [27] Exemption requests often reflected misconceptions about the vaccine and influenza. [27] Several requests cited chemotherapy or immuno-compromise as a reason not to get the influenza vaccine, even though these groups are at high risk for complications from influenza and are specifically recommended to be vaccinated. [27] Several requests cited pregnancy, although the influenza vaccine is recommended during pregnancy. [27]

Similarly, a five-year study of mandatory influenza vaccination of approximately 5,000 healthcare workers from Virginia Mason Medical Centre sustained influenza vaccination rates of more than 98% during 2005-2010. [28] Less than 0.7% of healthcare workers were granted exemption for medical or religious reasons and were required to wear a mask at work during influenza season, and less than 0.2% of

healthcare workers refused vaccination and left the centre. [28]

Conclusion

Mandatory annual influenza vaccination of healthcare workers raises complex professional and ethical issues. However, the arguments in favour are clear. 1. Seasonal influenza is a serious and potentially fatal disease, associated with considerable morbidity and mortality among the elderly, neonates, immuno-compromised and patients with chronic diseases. [4] 2. The influenza vaccine has been evaluated for safety, quality, effectiveness and cost-effectiveness for its intended use in the Australian population. [9] 3. Healthcare workers themselves may potentially act as vectors for nosocomial transmission of seasonal influenza and this risk to patients can be reduced by safe, effective annual influenza vaccination of healthcare workers. [10] 4. The contagious period of seasonal influenza begins before symptoms appear and the virus may be shed for at least one day prior to symptomatic illness. [14] 5. Influenza vaccination of healthcare workers may reduce the risk of seasonal influenza outbreaks in all types of health care settings and has been specifically shown to significantly reduce morbidity and mortality. [12] 6. Seasonal influenza contributes an enormous economic burden to society from the loss of working time/productivity associated with influenza-related work absence and increased use of medical resources required to treat patients with influenza and its complications. [19] 7. Traditional strategies to improve uptake by healthcare workers consistently fail, with only 35% to 40% of healthcare workers vaccinated annually. [8] 8. Mandatory influenza vaccination programs with medical and religious exemptions have successfully increased annual influenza vaccination rates of healthcare workers to >98%. [27,28] 9. Exemption requests often reflected misconceptions about the vaccine and influenza, and reflect the importance of continuous education programs and the need for a better understanding of the reasons for compliance with influenza vaccination. [27 22]

These facts suggest that mandatory annual influenza vaccination of healthcare workers is ethically justified and, if implemented

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appropriately, will be acceptable. [15] For this to occur, a mandatory program needs leadership by senior clinicians and administrators; consultation with healthcare workers and professional organisations; appropriate education; free, easily accessible influenza vaccine and adequate resources to deliver the program efficiently. It further requires provision for exemptions on medical and religious grounds and appropriate sanctions for those who refuse annual influenza vaccination, for example, requirement to wear a mask during influenza season, or termination of employment. [15] Healthcare workers accept a range of moral and other professional responsibilities, including a duty to protect patients in their care from unnecessary harm, to do good, to respect patient autonomy, and to treat all patients fairly. They also accept reasonable, but not unnecessary, occupational risk such as exposure to infectious diseases. [15] Vaccination is often seen as something that people have a right to accept or refuse. However, freedom to choose also depends on the extent to which that choice affects others. [15] In the healthcare setting, the autonomy of healthcare workers must be balanced against patients' rights to protection from avoidable harm, and the moral obligation of healthcare workers not to put others at risk. [15] Mandatory annual influenza vaccination of healthcare workers is consistent with the right the public have to expect that healthcare workers will take all necessary and reasonable precautions to keep them safe and minimise harm. [15] Traditional strategies to improve uptake by healthcare workers are minimally effective, expensive, and inadequate to protect patient safety. Therefore, low voluntary influenza vaccination rates of healthcare workers leave only one option to protect the public: mandatory annual influenza vaccination of healthcare workers.

Conflicts of interest

None declared.

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Suxamethonium versus rocuronium in rapid sequence induction: Dispelling the common myths

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Rapid sequence induction (RSI) is a technique used to facilitate endotracheal intubation in patients at high risk of aspiration and for those who require rapid securing of the airway. In Australia, RSI protocols in emergency departments usually dictate a predetermined dose of an induction agent and a neuromuscular blocker given in rapid succession. Suxamethonium, also known as succinylcholine, is a depolarising neuromuscular blocker (NMB) and is commonly used in RSI. Although it has a long history of use and is known for producing good intubating conditions in minimal time, suxamethonium possesses certain serious side effects and contraindications (that are beyond the scope of this article).

If there existed no alternative NMB, then the contraindications associated with suxamethonium would be irrelevant – yet there exists a suitable alternative. Rocuronium, a non-depolarising NMB introduced into Australia in 1996, has no known serious side effects or contraindications (excluding anaphylaxis). Unfortunately, many myths surrounding the properties of rocuronium have propagated through the anaesthesia and emergency medicine communities, and have resulted in some clinicians remaining hesitant to embrace this drug as a suitable alternative to suxamethonium for RSI. This essay aims to dispel a number of these myths through presenting the evidence currently available and thus allowing physicians to make informed clinical decisions that have the potential to significantly alter patient outcomes. It is not intended to provide a clear answer to the choice of NMB in RSI, but rather to encourage further debate and discussion on this controversial topic under the guidance of evidence-based medicine.

One of the more noteworthy differences between these two pharmacological agents is their duration of action. The paralysis induced by suxamethonium lasts for five to ten minutes, while rocuronium has a duration of action of 30-90 minutes, depending on the dose used. The significantly shorter duration of action of suxamethonium is often quoted by clinicians as being of great significance in their decision to utilise this drug. In fact, some clinicians are of the opinion that by using suxamethonium, they insert a certain 'safety margin' into the RSI protocol under the belief that the NMB will 'wear off' in time for the patient to begin spontaneously breathing again in the case of a failed intubation. Benumof *et al.* (1997) [1] explored this concept by methodically analysing the extent of haemoglobin desaturation (SpO_2) following administration of suxamethonium 1.0mg/kg in patients with a non-patent airway. This study found that critical haemoglobin desaturation will occur prior to functional recovery (that is, return of spontaneous breathing).

In 2001, a study by Heier *et al.* [2] was conducted, involving twelve healthy volunteers aged 18 to 45 years who were all pre-oxygenated to an end-tidal oxygen concentration >90% (after breathing a FiO_2 of 1.0 for three minutes). Following the administration of thiopental and suxamethonium 1.0mg/kg, no assisted ventilation was provided and the oxygen saturation levels were closely monitored. The results demonstrated that one third of the patients included in the study desaturated to SpO_2 <80% (at which point they received assisted ventilation during the trial). As the authors clearly stated, the study participants were all young, healthy and slim individuals who received optimal pre-oxygenation, yet still a significant proportion suffered critical haemoglobin desaturation before spontaneous ventilation



resumed. In a real-life scenario, particularly in the patient population who require RSI, an even higher number of patients would be expected to display significant desaturation due to their failing health and the limited time available to provide pre-oxygenation. Although one may be inclined to argue that the results would be altered by reducing the dose of suxamethonium, Naguib *et al.* [3] affirmed that, while reducing the dose from 1.0mg/kg to 0.6mg/kg did slightly reduce the incidence of SpO_2 <90% (from 85% to 65%), it did not shorten the time to spontaneous diaphragmatic movements. Therefore, the notion that the short duration of action of suxamethonium can be relied upon to improve safety in RSI is not supported and should not be trusted as a reliable means to rescue a "cannot intubate, cannot ventilate" situation.

Having demonstrated that differences in the duration of action should not sway one in the false belief of improving safety in RSI, let us compare the effect of the two drugs on oxygen saturation levels if apnoea was to occur following their administration. As suxamethonium is a depolarising agent, it has the side effect of muscle fasciculations following administration, whereas rocuronium, a non-depolarising agent, does not. It has long been questioned whether or not the existence of fasciculations associated with the use of suxamethonium alters the time to onset of haemoglobin desaturation if the airway was unable to be secure in a timely fashion and thus prolonged apnoea occurred.

This concept was explored by Taha *et al.* [4] who divided enrolled participants in the study into three groups: lidocaine/fentanyl/rocuronium, lidocaine/fentanyl/suxamethonium and propofol/suxamethonium. Upon measuring the time to onset of haemoglobin desaturation (deemed to be SpO_2 <95%), it was discovered that both groups receiving suxamethonium developed significantly faster desaturation than the group receiving rocuronium. By analysing the differences between the two groups receiving suxamethonium, one discovers a considerable difference in results, with the lidocaine/fentanyl group having a longer onset to desaturation than the propofol group. Since lidocaine and fentanyl are recognised to decrease (but not completely attenuate) the intensity of suxamethonium-induced fasciculations, these results suggested that the fasciculations associated with suxamethonium do result in a quicker onset to desaturation

compared to rocuronium.

Another recent study by Tang *et al.* [5] provides further clarification on this topic. Overweight patients with a BMI of 25-30 who were undergoing elective surgery requiring RSI were enrolled in the study. Patients were given either 1.5mg/kg suxamethonium or 0.9mg/kg rocuronium and no assisted ventilation was provided following induction until SpO₂ <92% (designated as the 'Safe Apnoea Time'). The time taken for this to occur was measured in conjunction with the time required to return the patient to SpO₂ >97% following introduction of assisted ventilation with FiO₂ of 1.0. The authors concluded that suxamethonium not only made the 'Safe Apnoea Time' shorter but also prolonged the recovery time to SpO₂ >97% compared to rocuronium. In summary, current evidence suggests that the use of suxamethonium results in a faster onset of haemoglobin desaturation than rocuronium, most likely due to the increased oxygen requirements associated with muscle fasciculations.

Since RSI is typically used in situations where the patient is at high risk of aspiration, the underlying goal is to secure the airway in the minimal amount of time possible. Thus, the time required for the NMB to provide adequate intubating conditions is of great importance, with a shorter time translating into better patient outcomes, assuming all other factors are equal. Suxamethonium has long been regarded as the 'gold-standard' in this regard, yet recent evidence suggests that the poor reputation of rocuronium in regards to the time required is primarily due to inadequate dosing. Recommended doses for suxamethonium tend to be reliably stated as 1.0-1.5mg/kg, [6] whereas rocuronium dosages have often been quoted as 0.6mg/kg, which, as will be established below, is inadequate for use in RSI.

A prospective, randomised trial study published by Sluga *et al.* [7] in 2005 concluded that, upon comparing intubating conditions following administration of either 1.0mg/kg suxamethonium or 0.6mg/kg rocuronium, there was a significant improvement in conditions with suxamethonium at 60 seconds post-administration. Another study [8] examined the frequency of good and excellent intubating conditions with rocuronium (0.6mg/kg and 1.0mg/kg) or suxamethonium (1.0mg/kg). Upon comparison of the groups receiving rocuronium, the 1.0mg/kg group had a consistently greater frequency of both good and excellent intubating conditions at 50 seconds. While the rocuronium 1.0mg/kg and suxamethonium 1.0mg/kg groups had a similar frequency of acceptable intubating conditions, there was a higher incidence of excellent conditions in the suxamethonium group. A subsequent study [9] confirmed this finding, with the intubating physician reporting a higher degree of overall satisfaction with the paralysis provided with suxamethonium 1.7mg/kg when compared to rocuronium 1.0mg/kg. In other words, it appears that the higher dose of 1.0mg/kg of rocuronium produces better intubating conditions than 0.6mg/kg, yet it does not do so to the same extent as suxamethonium.

If no evidence were available comparing an even higher dose of rocuronium, the argument for utilising suxamethonium in RSI would definitely be strengthened by the articles presented above. However, a retrospective evaluation of RSI and intubation from an emergency department in Arizona, United States provides further compelling evidence. [10] The median doses used were suxamethonium 1.65mg/kg (n=113) and rocuronium 1.19mg/kg (n=214) and the study authors state there was "no difference in success rate for first intubation attempt or number of attempts regardless of the type of paralytic used or the dose administered." To add further weight to this issue, a Cochrane Review in 2008 titled "Rocuronium versus succinylcholine for rapid sequence induction intubation" combined 37 studies for analysis and concluded that "no statistical difference in intubating conditions was found when [suxamethonium] was compared to 1.2mg/kg rocuronium." [11] Hence, there exists sufficient evidence that with adequate dosing, rocuronium (1.2mg/kg) is comparable to suxamethonium in time to onset of intubating conditions and thus this argument cannot be used to aid in selecting an appropriate neuromuscular blocker for RSI.

In recent times, particularly here in Australia, there have been questions posed regarding a supposedly increased risk of anaphylaxis to rocuronium. Rose *et al.* [12] from Royal North Shore Hospital in Sydney addressed this query in a paper in 2001. They found that the incidence of anaphylaxis to any NMB will be determined by its market share. Since the market share (that is, number of uses) of rocuronium is increasing, the cases of anaphylaxis are also increasing – but importantly, they are only increasing "in proportion to usage." Of note, the authors state that rocuronium should still be considered a drug of "intermediate risk" of anaphylaxis, compared to suxamethonium which is "high risk". Although not addressed in this paper, there are additional factors that have the potential to alter the incidence of anaphylaxis, such as geographical variation that may be related to the availability of pholcodine in cough syrup. [13]

Before the focus of this paper shifts to a novel agent that has the potential to significantly alter the decision of selecting between suxamethonium versus rocuronium in RSI, there remains a pertinent issue that needs to be discussed. It appears as though one of the key properties of suxamethonium is its brief duration of only five to ten minutes and many clinicians tend to quote this as an important aspect, with the Cochrane Review itself stating that "succinylcholine was clinically superior as it has a shorter duration of action," despite finding no statistical difference otherwise. [11]

The question that needs to be posed is whether this is truly an advantage of a NMB used in RSI. Patients who require emergency intubation often have a dire need for a secure airway to be established – simply allowing the NMB to "wear off" and the patient to begin spontaneously breathing again does nothing to alter their situation. One must consider that, even if the clinician was aware of the evidence against relying on suxamethonium's short duration of action to rescue them from a failed intubation scenario, the decision to initiate further measures (that is, progress to a surgical airway) would be delayed in such a scenario. If rocuronium, with its longer duration of action, was used, would clinicians then feel more compelled to 'act' rather than 'wait' in this rare scenario, knowing that the patient would remain paralysed? If rescue techniques such as a surgical airway were instigated, would the awakening of the patient (due to suxamethonium terminating its effect) be a hindrance? Although the use of rocuronium presents the risk of a patient requiring prolonged measures to maintain oxygenation and ventilation in a "cannot intubate, can ventilate" scenario, paralysis would be reliably maintained if a surgical airway was required.

No discussion on the debate of suxamethonium versus rocuronium would be complete without mentioning a new drug that appears to hold great potential in this arena – sugammadex. A γ -cyclodextrin specifically designed to encapsulate rocuronium and thus cause disassociation from the acetylcholine receptor, it acts to reverse the effects of neuromuscular blockade from rocuronium. In addition to its action on rocuronium, sugammadex also appears to have some crossover effect on vecuronium, another steroidal non-depolarising NMB. While acetylcholinesterase inhibitors are often used to reverse NMBs, they act non-specifically on both muscarinic and nicotinic synapses and cause many unwanted side effects. If they are given before there is partial recovery (>10% twitch activity) of neuromuscular blockade, they do not shorten the time to 90% recovery and thus are ineffective against profound block.

Sugammadex was first administered to human volunteers in 2005 with minimal side effects. [14] It displayed great potential in achieving quick recovery from rocuronium-induced paralysis within a few minutes. Further trials were conducted, including by de Boer *et al.* [15] in the Netherlands. Neuromuscular blockade was induced with rocuronium 1.2mg/kg and doses ranging from 2.0 to 16.0mg/kg of sugammadex given. With recovery of the train-of-four ratio to 0.9 designated as the primary outcome, the authors found that successive increases in the dose of sugammadex resulted in decreased time required to reverse profound blockade at five minutes following administration of rocuronium, with sugammadex 16mg/kg giving a mean recovery time

of only 1.9 minutes compared to the placebo recovery time of 122.1 minutes. In a review article, Mirakhur [16] further supported the use of high-dose sugammadex (16mg/kg) in a situation requiring rapid recovery of neuromuscular blockade.

With an effective reversal agent for rocuronium presenting a possible alternative to suxamethonium in rapid sequence inductions, Lee *et al.* [17] closely examined the differences in time to termination of effect. They studied 110 patients randomised to either rocuronium 1.2mg/kg or suxamethonium 1mg/kg. At three minutes following administration of rocuronium, 16mg/kg sugammadex was given. The results of this study confirmed the potential of sugammadex and its possible future role in RSI, as the study group given rocuronium and sugammadex (at three minutes) recovered significantly faster than those given suxamethonium (mean recovery time to first twitch 10% = 4.4 and 7.1 minutes respectively). The evidence therefore suggested that administering sugammadex 16mg/kg at three minutes after rocuronium 1.2mg/kg resulted in a shorter time to reversal of neuromuscular blockade compared to spontaneous recovery with suxamethonium. While sugammadex has certainly shown great potential, it remains an expensive drug and there still exist uncertainties regarding repeat dosing with rocuronium following reversal with sugammadex, [18] as well as the need to suitably educate and train staff on its appropriate

use, as demonstrated by Bisschops *et al.* [19] It is also important to note that for sugammadex to be of use in situations where reversal of neuromuscular blockade is required, the full reversal dose (16mg/kg) must be readily available. Nonetheless, it appears as if sugammadex may revolutionise the use of rocuronium not only in RSI, but also for other forms of anaesthesia in the near future.

As clinicians, we should strive to achieve the best patient outcomes possible. Without remaining abreast of the current literature, our exposure to new therapies will be limited and, ultimately, patients will not always be provided with the high level of medical care they desire and deserve. I urge all clinicians who are tasked with the difficult responsibility of establishing an emergency airway with RSI to consider rocuronium as a viable alternative to suxamethonium and to strive to understand the pros and cons associated with both agents, in order to ensure that an appropriate choice is made on the basis of solid evidence-based medicine.

Conflicts of interest

None declared.

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Ear disease in Indigenous Australians: A literature review

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Introduction

The Australian Indigenous versus non-Indigenous mortality gap is worse in Australia than in any other Organisation for Economic Co-operation and Development nation with disadvantaged Indigenous populations, including Canada, New Zealand, and the USA. [1] This gap reached a stark peak of seventeen years in 1996-2001. [2] Otitis media affects 80% of Australian children by the age of three years, being one of the most common diseases of childhood. [3]

Whilst ear diseases and their complications are now rarely a direct cause for mortality, especially since the advent of antimicrobial therapy and the subsequent reduction in extracranial and intracranial complications, [4] the statistics of ear disease nevertheless illustrate the unacceptable disparity between the health status of these two populations cohabiting a developed nation, and are an indictment of the poor living conditions in Indigenous communities. [5] Moreover, the high prevalence of ear disease among Aboriginal and Torres Strait Islanders is associated with secondary complications that represent significant morbidity within this population, most notably conductive hearing loss, which affects up to 67% of school-age Australian Indigenous children. [6]

This article aims to illustrate the urgent need for the development of appropriate strategies and programs, which are founded on evidence-based research and also integrate cultural consideration for, and design input from, the Indigenous communities, in order to reduce the medical and social burden of ear disease among Indigenous Australians.

Methodology

This review covered recent literature concerning studies of ear disease in the Australian Indigenous population. Medical and social science databases were searched for recent publications from 2000-2011. Articles were retrieved from The Cochrane Library, PubMed, Google Scholar and BMJ Journals Online. Search terms aimed to capture a broad range of relevant studies. Medical textbooks available at the medical libraries of Notre Dame University (Western Australia) and The University of Western Australia were also used. A comprehensive search was also made of internet resources; these sources included the websites of The Australian Department of Health and Ageing, the World Health Organisation, and websites of specific initiatives targeting ear disease in the Indigenous Australian population.

Peer reviewed scientific papers were excluded from this review if ear disease pertaining to Indigenous Australians was not a major focus of the paper. Studies referred to in this review vary widely in type by virtue of the multi-faceted topic addressed and include both qualitative and quantitative studies. For the qualitative studies, those that contributed new information or covered areas that had not been fully explored in quantitative studies were included. Quantitative studies with weaknesses arising from small sample size, few factors measured or weak data analysis were included only when they provided insights not available from more rigorous studies.

Overview and epidemiology

The percentage of Australian Indigenous children suffering otitis media and its complications is disproportionately high; up to 73% by the age of twelve months. [7] In the Australian primary healthcare setting, Aboriginal and Torres Strait Islander children are five times more



Otitis Media (OM) Definitions

- Acute otitis media (AOM) without perforation: The presence of middle ear fluid with symptoms or signs of suppurative infection, which may include otalgia, fever, irritability, vomiting or diarrhoea.
- Acute otitis media with perforation: Acute suppurative infection with recent discharge from the middle ear through a perforation or through a tympanostomy tube.
- Recurrent AOM (RAOM): Three recurrent episodes of AOM within six months, or four to five episodes in twelve months.
- Chronic suppurative otitis media (CSOM): Persistent discharge from the middle ear through a tympanic membrane perforation for more than six weeks, with or without acute or chronic otorrhoea.

likely to be diagnosed with severe otitis media than non-Indigenous children. [8]

Chronic suppurative otitis media (CSOM) is uncommon in developed societies and is generally perceived as being a disease of poverty. The World Health Organisation (WHO) states that a prevalence of CSOM greater than or equal to 4% indicates a massive public health problem of CSOM warranting urgent attention in targeted populations. [9] CSOM affects Indigenous Australian children up to ten times this proportion, [5] and fifteen times the proportion of non-Indigenous Australian children, [8] thus reflecting an unacceptably great dichotomy of the prevalence and severity of ear disease and its complications between Indigenous and non-Indigenous Australians.

Comparisons of the burden of mortality and the loss of disability-adjusted life years (DALYs) have been attempted between otitis media (all types grouped together) and illnesses of importance in developing countries. These comparisons show that the burden of otitis media is substantially greater than that of trachoma, and comparable with that of polio, [9] with permanent hearing loss accounting for a large proportion of this DALY burden.

Whilst there are some general indications that the health of Indigenous Australian children has improved over the past 30 years, such as increased birth weight and lower infant mortality, there is evidence to suggest that morbidities associated with infections such as respiratory

infections and otitis media have not changed. [10-12]

Middle Ear disease: Pathophysiology and host risk factors

The disease process of otitis media is a complex and dynamic continuum. [10] Hence there is inconsistency throughout the medical community regarding definitions and diagnostic criteria for this disease, and controversy regarding what constitutes “gold standard” treatment. [7,13] In order to form a discussion about the high prevalence of middle ear diseases in Indigenous Australians, one must first establish an understanding of their aetiology and pathogenicity.

Host-related risk factors for otitis media include young age, high rates of nasopharyngeal colonisation with potentially pathogenic bacteria, eustachian tube dysfunction and palato-facial abnormalities, lack of passive immunity and acquisition of respiratory tract infections in the early stages of life. [7,9,10,14,15]

Streptococcus pneumoniae, *Haemophilus influenzae* and *Moraxella catarrhalis* are the recognised major pathogens of otitis media. However, this disease has a complex, polymicrobial aetiology, with at least fifteen other genera having been identified in middle ear effusions. [11] The organisms involved in CSOM are predominantly opportunistic organisms, especially *Pseudomonas aeruginosa*, which is associated with approximately 20-50% of CSOM in both Aboriginal, Torres Strait Islander and non-Indigenous children. [10]

Relatively new findings in otitis media pathogenicity have included the identification of *Alloiococcus otitidis* and human metapneumovirus. [13] *A. otitidis* in particular, a slow-growing aerobic gram positive bacterium, has been identified in as many as 20-30% of middle ear effusions in children with CSOM. [13,16,17] The importance of interaction between viruses and bacteria (with the major identified viruses being adenovirus, rhinovirus, polyomavirus and more recently human metapneumovirus) is well recognised in the pathogenicity of otitis media. [13,18,19] High identification rates of viral-bacterial co-infection found in asymptomatic children with otitis media (42% Indigenous and 32% non-Indigenous children) underscore the potential value in preventative strategies targeted at specific pathogens. [19]

The role of biofilms in otitis media pathogenesis has been of great interest since a fluorescence in-situ hybridisation study detected biofilms in 92% of middle ear mucosal biopsies from 26 children with recurrent otitis media or otitis media with effusion. [20] This suggested an explanation for the persistence and recalcitrance of otitis media, as bacteria growing in biofilm are more resistant to antibiotics than planktonic cells. [20]

However, translating all this knowledge into better health outcomes - by means of individual clinical treatment and community preventative strategies - is not straightforward. A more thorough understanding of the polymicrobial pathogenesis is needed if more effective therapies for otitis media are to be achieved.

Some research has been involved in the possibility of a genetic predisposition to otitis media, based on its high prevalence observed across several Indigenous populations around the world, including the Indigenous Australian, Inuit, Maori and Native American peoples. [10] However, whilst the suggestion that genetic factors may play a role in otitis media susceptibility is a worthwhile area of further research, its emphasis should not overlook the significance of poverty, which generally exists throughout colonised Indigenous populations worldwide and is a major public health risk factor. It should be remembered that socioeconomic status is a major determinant of disparities in Indigenous health, irrespective of genetics or ethnicity.

Environmental risk factors

The environmental risk factors for otitis media are well recognised and extensively documented. They include season, inadequate housing, overcrowding, poor hygiene, lack of breastfeeding, pacifier use, poor nutrition, exposure to cigarette or wood-burning smoke, poverty and inadequate or unavailable health care. [5,7,9,10,21]

Several recent studies have examined the impact of overcrowding and poor housing conditions on the health of Indigenous children, with a particular focus on upper respiratory tract infections and ear disease. [22-24] The results of these studies reinforced the belief that elements of the household and community environment are important underlying determinants of the occurrence of common childhood conditions, which impair child growth and development, contribute to the risk of chronic disease and to the seventeen year gap in life expectancy between Aboriginal and Torres Strait Islander people and non-Indigenous Australians. [22, 23] Interestingly, one study's findings identified the potential need for interventions which could target factors that negatively impact the psychosocial status of carers and which could also target health-related behaviour, including maintenance of household and personal hygiene. [22]

Raised levels of stress and poor mental health associated with the psycho-spatial elements of overcrowded living (that is, increased interpersonal contact, lack of privacy, loss of control, high demand, noise, lack of sleep) may therefore be considered as having a negative impact on the health of dwellers, especially those whose health largely depends on care from others, such as the elderly and young children, who are more susceptible to disease. Urgent attention is needed to improve housing and access to clean running water, nutrition and quality of care, and to give communities greater control over these improvements.

Exposure to environmental smoke is another significant, yet potentially preventable, risk factor for respiratory infections and otitis media in Indigenous children. [25,26] Of all the environmental risk factors for otitis media mentioned above, environmental smoke exposure is arguably the most readily amenable to modification. A recent randomised controlled trial tested the efficacy of a family-centred tobacco control program, aimed at reducing the incidence of respiratory disease among Indigenous children in Australia and New Zealand. It was found that interventions aimed at encouraging smoking cessation as well as reducing exposure of Indigenous children to environmental smoke had the potential for significant benefit, especially when the intervention designs included culturally sound, intensive family-centred programs that emphasised capacity-building of the Indigenous community. [25] Such studies testify to the potentially high levels of interest, cooperativeness, pro-activeness and compliance demonstrated by Indigenous communities regarding public health interventions, given the study design is culturally appropriate and accepts that Indigenous people need to be meaningfully engaged in preventative health efforts.

Preventative strategies

The advent of the 7-valent pneumococcal conjugate vaccine has seen a substantial decrease in invasive pneumococcal disease. However, changing patterns of antibiotic resistance and pneumococcal serotype replacement have been documented since the introduction of the vaccine, and large randomised controlled trials have shown its reduction of risk of acute otitis media and tympanic membrane perforation to be minimal. [13,27] One retrospective cohort study's data suggested that the pneumococcal immunisation program may be unexpectedly increasing the risk of acute lower respiratory infection (ALRI) requiring hospitalisation among vaccinated children, especially after administration of the 23vPPV booster at eighteen months of age. [28] These findings warrant re-evaluation of the pneumococcal immunisation program and further research into alternative medical prevention strategies.

Swimming pools in remote communities have been associated with reduced prevalence of tympanic membrane perforations (as well as pyoderma), indicating the long term benefits associated with reduction in chronic disease burden and improved educational and social outcomes. [6] No outbreaks of infectious diseases have occurred in the swimming pool programmes to date and water quality is regularly monitored according to government regulations. On the

condition that adequate funding continues to maintain high safety and environmental standards of community swimming pools, their net effect on community health will remain positive and worthwhile.

Treatment: Current guidelines and practices, potential future treatments

Over the last ten years there has been a general tendency to reduce immediate antibiotic treatment for otitis media for children aged over two years, with the “watchful waiting” approach having become more customary among primary care practitioners. [7] The current therapeutic guidelines note that antibiotic therapy provides only modest benefit for otitis media, with sixteen children requiring treatment at first presentation to prevent one child experiencing pain at two to seven days. [29] Routine antibiotics are recommended only for infants less than six months and for all Aboriginal and Torres Strait Islander children at the initial presentation of acute otitis media. [8] Current guidelines acknowledge that suppurative complications of otitis media are common among Indigenous Australians; hence specific therapeutic guidelines apply to these patients. [30] For those patients in whom antibiotics are indicated, a twice-daily regimen, five day course of amoxicillin is the antibiotic agent of choice. Combined therapy with a seven day course of higher-dose amoxicillin and clavulanate is recommended for poor response to amoxicillin or patients in high-risk populations for amoxicillin-resistant *Streptococcus pneumoniae*. For CSOM, topical ciprofloxacin drops are now approved for use in Aboriginal and Torres Strait Islander children, since a study in 2003 contributed to their credibility in the treatment of CSOM. [31,32]

Treatment failure with antibiotics has been observed in some Aboriginal and Torres Strait Islander communities due to poor adherence to the twice-daily regimen of five and seven day courses of amoxicillin. [33] The reasons for non-adherence remain unclear. They may relate to language barriers (misinterpretation or non-comprehension of instructions regarding antibiotic use), storage (lacking a home fridge in which to keep the antibiotics), shared care of the child patient (rather than one guardian) or remoteness (reduced access to healthcare facility and reduced likelihood of follow-up). Treatment failure with antibiotics has also been noted in cases of optimal compliance in Indigenous communities, indicating that poor clinical outcomes may also be due to organism resistance and/or pathogenic mechanisms. [11]

A recent study compared the clinical effectiveness of a single-dose azithromycin treatment with the recommended seven day course of amoxicillin among Indigenous children with acute otitis media in rural and remote communities in the Northern Territory. [33] Whilst azithromycin was found to be more effective at eradicating otitis media pathogens than amoxicillin, azithromycin treatment was associated with an increase in carriage of azithromycin-resistant *Streptococcus pneumoniae*. Another recent study investigated the antimicrobial susceptibility of *Moraxella catarrhalis* isolated from a cohort of children with otitis media in the Kalgoorlie-Boulder region of Western Australia. [34] It was found that a large proportion of strains were resistant to ampicillin and/or co-trimoxazole. Findings from studies such as these indicate that the current therapeutic guidelines, which recommend amoxicillin as the antibiotic of choice for treatment of otitis media, may require revision.

Overall, further research is needed to determine which antibiotics best eradicate otitis media pathogens and reduce bacterial load in the nasopharynx in order to achieve better clinical outcomes. Recent studies indicate that currently recommended antibiotics may need to be reviewed in light of increasing rates of resistant organisms and emerging evidence of new organisms.

Social ramifications associated with ear disease

There is substantial evidence to demonstrate that ear disease has a significant negative impact on the developmental future of Aboriginal and Torres Strait Islander children. [35] Children who are found to have early-onset otitis media (under twelve months) are at high risk

of developing long-term speech and language problems secondary to conductive hearing loss, with the specific areas of cognition thought to be affected being auditory processing, attention, behaviour, speech and language. [36] Between 10% and 67% of Indigenous Australian school age children have perforated tympanic membranes, and 14% to 67% have some degree of hearing loss. [37]

Sub-optimal hearing can be a serious handicap for Indigenous children who begin school with delayed oral skills, especially if English is not their first language. Learning the phonetics and grammar of a second language with the unrecognised disability of impaired hearing renders the classroom experience a difficult and unpleasant one for the student, resulting in reduced concentration and increased distractibility, boredom and non-attendance. Truancy predisposes to anti-social behaviour, especially among adolescents, who by this age tend to no longer have infective ear disease but do have established permanent hearing loss. [38] Poor engagement in education and employment, alcohol-fuelled interpersonal violence, domestic violence, and communication difficulties with police and in court have all been linked to the disadvantage of hearing loss and the eventuation of becoming involved in the criminal justice system. [39]

In the Northern Territory, where the Indigenous population accounts for only 30% of the general population, 82% of the 1100 inmates in Northern Territory correctional facilities in the year 2010 were found to be Aboriginal or Torres Strait Islander. [40] Two recent studies conducted within the past two years investigated the prevalence of hearing loss among inmates in Northern Territory correctional facilities. They found that more than 90% of Australian Indigenous inmates had a significant hearing loss of >25dB. [39] A third study in a youth detention centre in the Northern Territory demonstrated that as many as 90% of Australian Indigenous youth in detention may have hearing loss, [41] whilst yet another study found that almost half the female Indigenous inmates at a Western Australian prison had significant hearing loss, almost ten-fold that of the non-Indigenous inmates. [37]

The fact that the Northern Territory study of adult inmates showed a comparatively low prevalence of hearing loss among Indigenous persons who weren't imprisoned (33% not imprisoned compared with 94% imprisoned) [39] demonstrates a strong correlation between the high prevalence of hearing loss and the over-representation of Indigenous people in Australian correctional facilities. Although this area warrants further research, the data from these studies demonstrate that the higher prevalence of hearing loss among Indigenous inmates suggests that ear disease and hearing loss may have played a role in many Aboriginal and Torres Strait Islander people becoming inmates.

Changes and developments for the future

As we have discussed throughout this article, the unacceptably high burden of ear disease among Indigenous Australians is due to a myriad of medical, biological, socio-cultural, pedagogical, environmental, logistical and political factors. All of these contributing factors must be addressed if a reduction in the morbidity and social ramifications associated with ear disease among Indigenous Australians is to be achieved. The great dichotomy in health service provision could eventually be eradicated if there is the political will and sufficient, specific funding.

Addressing these factors will require the integration of multi-disciplinary efforts from medical researchers, health care practitioners, educational professionals, correctional facilities, politicians, and most importantly the members of Indigenous communities. The latter's active involvement in, and responsibility for, community education, prevention and medical management of ear disease are imperative to achievement of these goals.

The Government's response to a recent federal Senate inquiry into Indigenous ear health included \$47.7 million over four years to support changes to the Australian Government's Hearing Services Program

(HSP). This was in addition to other existing funds available to eligible members of the hearing-impaired, such as the More Support for Students with Disabilities Initiative and the Better Start for Children With a Disability intervention. [42] Whilst this addition to the federal budget may be seen as a positive step in the Government's agenda to ameliorate the burden of ear health among the Indigenous Australian population, it will not serve any utility if the funding is not sustainably invested and effectively implemented along the appropriate avenues, which should:

1. Specifically target and reduce identified risk factors of otitis media.
2. Support the implementation of effective, evidence-based, public health prevention strategies, and encourage community control over improvements to education, employment opportunities, housing infrastructure and primary healthcare services.
3. Support constructive and practical multidisciplinary research into the areas of pathogenicity, diagnosis, treatment, vaccines, risk factors and prevention strategies of otitis media.
4. Support and encourage training and employment for healthcare and educational professionals in regional and remote areas. These professionals include doctors, audiologists, speech pathologists, and teachers, and all of these professions should offer programs that increase the number of practising Aboriginal and Torres Strait Islander clinicians and teachers.
5. Adequately fund ear disease prevention and medical treatment programs, including screening programs, so that they may expand, increase in their number and their efficacy. Such services should concentrate on prevention education, accurate diagnosis, antibiotic treatment, surgical intervention (where applicable) and scheduled follow-up of affected children. An exemplary program is Queensland's "Deadly Ears" program. [43]
6. Support the needs of students and inmates with established hearing loss in the educational and correctional environments,

for example, through provision of multidisciplinary healthcare services and the use of sound field systems with wireless infrared technology.

7. Support community and family education regarding the effects of hearing loss on speech, language and education.

All of these objectives should be fulfilled by cost-effective, sustainable, culturally-sensitive means. It is of paramount importance that these objectives should be well-received by, and include substantial input from, Indigenous members of the community. Successful implementation of these objectives reaching the grass-roots level (thus avoiding the so-called "trickle-down" effect) will not only require substantially increased resources, but also the involvement of Indigenous community members in intervention design and deliverance.

Conclusion

Whilst there remains a continuous need for valuable research in the area of ear disease, it appears that failure to apply existing knowledge is currently more of a problem than a dearth of knowledge. The design, funding and implementation of prevention strategies, community education, medical services and programs, and modifications to educational and correctional settings should be the current priorities in the national agenda addressing the burden of ear disease among Aboriginal and Torres Strait Islander people.

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Conflicts of interest

None declared.

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The future of personalised cancer therapy, today

May YW Wong

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May wrote this review after her oncology rotation, during which she witnessed patients, doctors and medical students alike being faced with a multitude of new anti-cancer drugs. She believes that it is important to be critical in one's approach to the promises, as well as pitfalls, of personalised cancer therapy in our era of the genetic revolution.

With the human genome sequenced a decade ago and the concurrent development of genomics, pharmacogenetics and proteomics, the field of personalised cancer treatment appears to be a maturing reality. It is recognised that the days of 'one-size-fits-all' and 'trial and error' cancer treatment are numbered, and such conventional approaches will be refined. The rationale behind personalised treatment is to target the genomic aberrations driving tumour development while reducing drug toxicity due to altered drug metabolism encoded by the patients' genome. That said, a number of key challenges, both scientific and non-scientific, must be overcome if we are to fully exploit knowledge of cancer genomics to develop targeted therapeutics and informative biomarkers. The progress of research has yet to be translated to substantial clinical benefits, with the exception of a handful of drugs (tamoxifen, imatinib, trastuzumab). It is only recently that new targeted drugs have been integrated into the clinical armamentarium. So the question remains: Will there be a day when doctors no longer make treatment choices based on population-based statistics but rather on the specific characteristics of individuals and their tumours?



Introduction

In excess of 100,000 new cases of cancer were diagnosed in Australia in 2010, and the impact of cancer care on patients, their carers, and the Australian society is hard to ignore. Cancer care itself consumes \$3.8 billion per year in Australia, constituting close to one-tenth of the annual health budget. [1] As such, alterations to our approach to cancer care will have wide-spread impacts on the health of individuals as well as on our economy. The first 'golden era' of cancer treatment began in the 1940s, with the discovery of the effectiveness of the alkylating agent, nitrogen mustard, against non-Hodgkin's lymphoma. [2] Yet the landmark paper that demonstrated cancer development required more than one gene mutation was published only 25 years ago. [3] With the discovery of the human genome sequence, [4] numerous genes have been implicated in the development of cancer. Data from The Cancer Genome Atlas (TCGA) [5] and the International Cancer Genome Consortium (ICGC) [6] reveal that even within a cancer subtype, the mutations driving oncogenesis are diverse.

The more we learn about the molecular basis of carcinogenesis, the more the traditional paradigm of chemotherapy 'cocktails' classified by histomorphological features appears inadequate. In many instances, this classification system correlates poorly with treatment response, prognosis and clinical outcome. Patients within a given diagnostic category receive the same treatment despite biological heterogeneity, meaning that some with aggressive disease may be undertreated, and some with indolent disease may be overtreated. In addition, these generalised cytotoxic drugs have many side effects, a low specificity, low concentration being delivered to tumours, and the development of resistance, which is an almost universal feature of cancer cells.

In theory, personalised treatment involves targeting the genomic aberrations driving tumour development while reducing drug toxicity due to altered drug metabolism encoded by the patient's genome. The outgrowth of innovations in cancer biotechnology and computational science has enabled the interrogation of the cancer genome and examination of variation in germline DNA. Yet there remain many

unanswered questions about the efficacy of personalised treatment and its applicability in clinical practice, which this review will address. The transition from morphology-based to a genetics-based taxonomy of cancer is an alluring revolution, but not without its challenges.

This article aims to outline the current methods in molecular profiling, explore the range of biomarkers available, examine the application of biomarkers in cancers common to Australia, such as melanoma and lung cancer, and to investigate the implications and limitations of personalised medicine in a 21st century context.

Genetic profiling of the cancer genome

We now know that individual tumour heterogeneity results from the gradual acquirement of genetic mutations and epigenetic alterations (changes in DNA expression that occur without alterations in DNA sequence). [7,8] Chromosomal deletions, rearrangements, and gene mutations are selected out during tumour development. These defects, known as 'driver' mutations, ultimately modify protein signalling networks and create a survival advantage for the tumour cell. [8-10] As such, pathway components vary widely among individuals leading to a variety of genetic defects between individuals with the same type of cancer.

Such heterogeneity necessitates the push for a complete catalogue of genetic perturbations involved in cancer. This need for a large-scale analysis of gene expression has been realised by current high throughput technologies such as DNA array technology. [11,12] Typically, a DNA array is comprised of multiple rows of complementary DNA (cDNA) samples lined up in dots on a small silicon chip. Today, arrays for gene expression profiling can accommodate over 30,000 cDNA samples. [13] Pattern recognition software and clustering algorithms promote the classification of tumour tissue specimens with similar repertoires of expressed genes. This has led to an explosion of genome-wide association studies (GWAS) which have identified new chromosomal regions and DNA variants. This information has been used to develop multiplexed tests that hunt for a range of possible mutations in an individual's cancer, to assist clinical decision-making. The HapMap aims to identify the millions of single nucleotide polymorphisms (SNPs), which are single nucleotide differences in the DNA sequence, which may confer individual differences in susceptibility to disease. The HapMap has identified low-risk genes for breast, prostate and colon cancers. [14] TCGA and ICGC have begun cataloguing significant

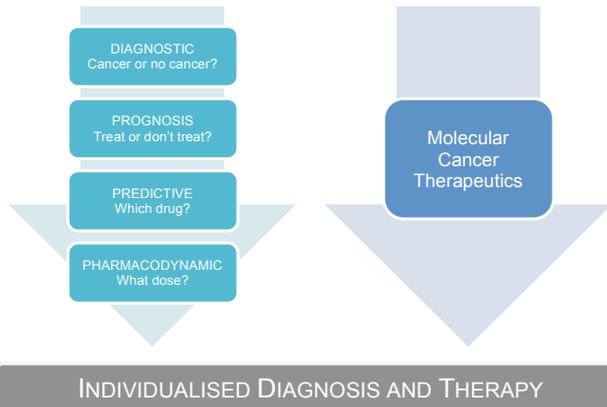


Figure 1. The use of biomarkers in cancer care. The two steps in this process are: (1) The successful development of diagnostic, prognostic, predictive and pharmacodynamic biomarkers; and (2) Effective molecularly-targeted therapeutics. This results in individualised diagnosis and therapy based on the molecular profile of the patient.

mutation events in common cancers. [5,6] OncoMap provides such an example, where alterations in multiple genes are screened by mass spectrometry. [15]

The reproduction and accuracy of microarray data needs to be addressed cautiously. ‘Noise’ from analysing thousands of genes can lead to false predictions and, as such, it is difficult to compare results across microarray studies. In addition, cancer cells alter their gene expression when extrapolated from their environment, potentially yielding misleading results. The clinical utility of microarrays is difficult to determine, given the variability of the assays themselves as well as the variability between patients and between the laboratories performing the analyses.

Types of cancer biomarkers

This shift from entirely empirical cancer treatment to stratified and eventually personalised approaches requires the discovery of biomarkers and the development of assays to detect them (Table 1). With recent technological advances in molecular biology, the range of cancer biomarkers has expanded, which will aid the implementation of effective therapies into the clinical armamentarium (Figure 1). However, during the past two decades, fewer than twelve biomarker assays have been approved by the US Food and Drug Administration (FDA) for monitoring response, surveillance or the recurrence of cancer. [16]

Early detection biomarkers

Most current methods of early cancer detection, such as mammography or cervical cytology, are based on anatomic changes in tissues or morphologic changes in cells. Various molecular markers, such as protein or genetic changes, have been proposed for early cancer detection. For example, PSA is secreted by prostate tissue and has been approved for the clinical management of prostate cancer. [17] CA-125 is recognised as an ovarian cancer-specific protein. [18]

Table 1. Available cancer biomarker at different clinical timepoints.

Type of Biomarker	Utility
Early detection	To screen patients to find cancer early
Diagnostic	To assess the presence or absence of cancer
Prognostic	To assess the survival probabilities of patients To determine the natural course of the cancer
Predictive	To predict whether the drug and other therapies will be effective
Pharmacodynamics	To calculate the effective dose of a drug

Diagnostic biomarkers

Examples of commercial biomarker tests include the Oncotype DX biomarker test and MammaPrint test for breast cancer. Oncotype DX is designed for women newly diagnosed with oestrogen-receptor (ER) positive breast cancer which has not spread to lymph nodes. The test calculates a ‘recurrence score’ based on the expression of 21 genes. Not covered by Medicare, it will cost US\$4,075 for each woman. One study found that this test persuaded oncologists to alter their treatment recommendations for 30% of their patients. [19]

Prognostic biomarkers

The tumour, node, metastasis (TNM)-staging system is the standard for prediction of survival in most solid tumours based on clinical, gross and pathologic criteria. Additional information can be provided with prognostic biomarkers, which indicate the likelihood that the tumour will return in the absence of any further treatment. For example, for patients with metastatic nonseminomatous germ cell tumours, serum-based biomarkers include α -fetoprotein, human chorionic gonadotropin, and lactate dehydrogenase.

Predictive biomarkers

Biomarkers can also prospectively predict response (or lack of response) to specific therapies. The widespread clinical usage of ER and progesterone receptors (PR) for treatment with tamoxifen, and human epidermal growth factor receptor-2 (HER-2) for treatment with trastuzumab, is evidence of the usefulness of predictive biomarkers.

Epidermal growth factor receptor (EGFR) is overexpressed in multiple cancer types. EGFR mutation is a strong predictor of a favourable outcome if treated with EGFR tyrosine kinase inhibitors such as gefitinib in non-small cell lung carcinoma (NSCLC) and anti-EGFR monoclonal antibodies such as cetuximab or panitumumab in colorectal cancer. [20] Conversely, the same cancers with KRAS mutations are associated with primary resistance to EGFR tyrosine kinase inhibitors. [21,22] This demonstrates that biomarkers, such as KRAS mutation status, can predict which patient may or may not benefit from anti-EGFR therapy (Figure 2).

Pharmacodynamic biomarkers

Determining the correct dosage for the majority of traditional

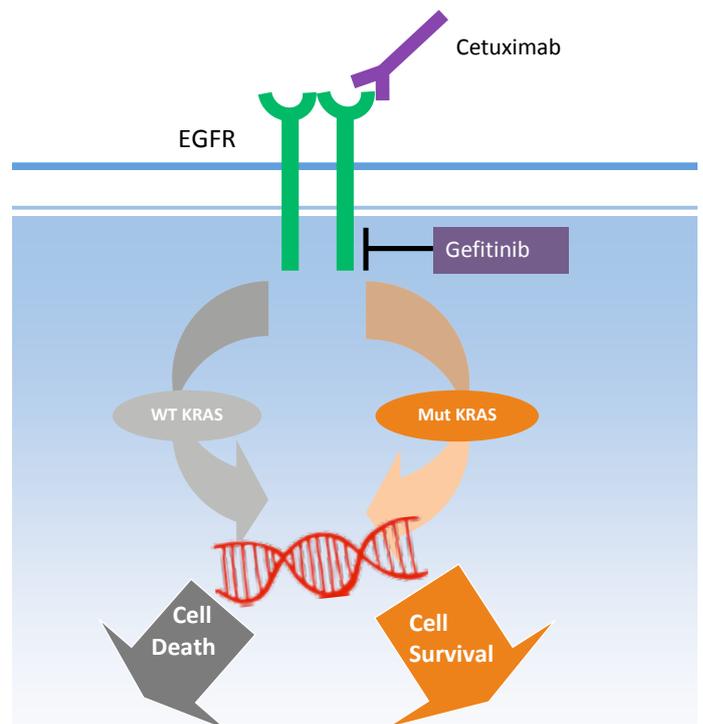


Figure 2. The relationship between anti-EGFR therapy and KRAS mutations. WT KRAS = Wild Type KRAS; Mut KRAS = Mutation KRAS.

chemotherapeutic agents presents a challenge because most drugs have a narrow therapeutic index. Pharmacodynamic biomarkers, in theory, can be used to guide dose selection. The magnitude of BCR–ABL kinase activity inhibition was found to correlate with clinical outcome, possibly justifying the personalised selection of drug dose. [23]

The role of biomarkers in common cancers

Biomarkers currently have a role in the prediction or diagnosis of a number of common cancers (Table 2).

Breast Cancer

Breast cancer can be used to illustrate the contribution of molecular diagnostics to personalised treatment. Discovered in the 1970s, tamoxifen was the first targeted cancer therapy against the oestrogen signalling pathway. [8] Approximately three quarters of breast cancer tumours express hormone receptors for oestrogen and/or progesterone. Modulating either the hormone ligand or the receptor has been shown to be effective in treating hormone receptor-positive breast cancer for over a century. Although quite effective for a subset of patients, this strategy has adverse partial oestrogenic effects in the uterus and vascular system, resulting in an increased risk of endometrial cancer and thromboembolism. [9,10] Alternative approaches to target the ligand production instead of the ER itself was hypothesised to be more effective with fewer side effects. Recent data suggest that the use of specific aromatase inhibitors (anastrozole, letrozole and exemestane), which block the formation of endogenous oestrogen, may be superior in both the adjuvant [24] and advanced disease settings. [25]

Lung Cancer

Lung cancer is the most common cause of cancer-related mortality affecting both genders in Australia. [26] Many investigators are using panels of serum biomarkers in an attempt to increase sensitivity of prediction. Numerous potential DNA biomarkers such as the overactivation of oncogenes, including K-ras, myc, EGFR, and Met, or the inactivation of tumour suppressor genes, including p53 and Rb, are being investigated. Gefitinib was found to be superior to carboplatin–paclitaxel in EGFR-mutant non-small cell lung cancer cases [20] and to improve progression-free survival, with acceptable toxicity, when compared with standard chemotherapy. [27]

Melanoma

Australia has the highest skin cancer incidence in the world. [28] Approximately two in three Australians will be diagnosed with skin cancer before the age of 70. [29] Currently, the diagnosis and prognosis of primary melanoma is based on histopathologic and clinical factors. In the genomic age, the number of modalities for identifying and subclassifying melanoma is rapidly increasing. These include immunohistochemistry of tissue sections and tissue microarrays and molecular analysis using RT-PCR, which can detect relevant multidrug resistance-associated protein (MRP) gene expression and characterisation of germ-line mutations. [30] It is now known that most malignant melanomas have a V600E BRAF mutation. [31] Treatment of metastatic melanoma with PLX4032 resulted in complete

or partial tumour regression in the majority of patients. Responses were observed at all sites of disease, including the bone, liver, and small bowel. [32]

Leukaemia

Leukaemia has progressed from being seen merely as a disease of the blood to one that consists of 38 different subtypes. [33] Historically a fatal disease, chronic myeloid leukaemia (CML) has been redefined by the presence of the Philadelphia chromosome. [34] In 1998, imatinib was marketed as a tyrosine kinase inhibitor. This drug has proven to be so effective that patients with CML now have mortality rates comparable to those of the general population. [35]

Colon Cancer

Cetuximab was the first anti-EGFR monoclonal antibody approved in the US for the treatment of colorectal cancer, and the first agent with proven clinical efficacy in overcoming topoisomerase I resistance. [22] In 2004, bevacizumab was approved for use in the first-line treatment of metastatic colorectal cancer in combination with 5-fluorouracil-based chemotherapy. Extensive investigation since that time has sought to define bevacizumab's role in different chemotherapy combinations and in early stage disease. [36]

Lymphoma

Another monoclonal antibody, rituximab, is an anti-human CD20 antibody. Rituximab alone has been used as the first-line therapy in patients with indolent lymphoma, with overall response rates of approximately 70% and complete response rates of over 30%. [37,38] Monoclonal antibodies directed against other B-cell-associated antigens and new anti-CD20 monoclonal antibodies and anti-CD80 monoclonal antibodies (such as galiximab) are being investigated in follicular lymphoma. [39]

Implication and considerations of personalised cancer treatment

Scientific considerations

Increasing information has revealed the incredible complexity of the cancer tumorigenesis puzzle; there are not only point mutations, such as nucleotide insertions, deletions and SNPs, but also genomic rearrangements and copy number changes. [40-42] These studies have documented a pervasive variability of these somatic mutations, [7,43] so that thousands of human genomes and cancer genomes need to be completely sequenced to have a complete landscape of causal mutations. And what about epigenetic and non-genomic changes? While there is a lot of intense research being conducted on the sorts of molecular biology techniques discussed, none have been prospectively validated in clinical trials. In clinical practice, what use is a 'gene signature' if it provides no more discriminatory value than performance status or TNM-staging?

Much research has so far been focused on primary cancers; what about metastatic cancers, which account for considerable mortality? The inherent complexity of genomic alterations in late-stage cancers, coupled with interactions that occur between tumour and stromal

Table 2. Clinically relevant biomarkers

Tumour type	Molecular Target	Biomarker	Biomarker type	Treatment
Breast cancer	HER2	HER-2 expression	Prognostic and predictive	Trastuzumab
Breast cancer	ER/PR	ER/PR expression	Prognostic and predictive	Tamoxifen
Colorectal cancer	EGFR1	KRAS mutation	Prognostic and predictive	Panitumumab, cetuximab
Lung cancer	EGFR1	EGFR mutation	Predictive	Erlotinib, gefitinib
Renal cell carcinoma	VEGF	VEGF		Sunitinib, everolimus
Gastrointestinal stromal tumour	c-KIT	c-KIT mutation	Predictive	Imatinib
Melanoma	BRAF	BRAF point mutation	Predictive	PLX4032
Leukaemia (chronic myeloid leukaemia)	BCR-ABL	BCR-ABL translocation	Predictive	Imatinib, nilotinib, dasatinib

cells, means that most often we are not measuring what we are treating. If we choose therapy based on the primary tumour, but we are treating the metastasis, we are likely giving the wrong therapy. Despite our increasing knowledge about metastatic colonisation, we still hold little understanding of how metastatic tumour cells behave as solitary disseminated entities. Until we identify optimal predictors for metastases and an understanding of the establishment of micrometastases and activation from latency, personalised therapy should be used sagaciously.

In addition, from a genomic discovery, it is difficult, costly and time-consuming to deliver to patients a new targeted therapy with suitable pharmacokinetic properties, safety and demonstrable efficacy in randomised clinical trials. The first cancer-related gene mutation was discovered nearly thirty years ago - a point mutation in the HRAS gene that causes a glycine-to-valine mutation at codon twelve. [44,45] The subsequent identification of similar mutations in the KRAS family [46-48] ushered in a new field of cancer research activity. Yet it is only now, three decades later, that KRAS mutation status is affecting cancer patient management as a 'resistance marker' of tumour responsiveness to anti-EGFR therapies. [21]

Ethical and Moral Considerations

The social and ethical implications of genetic research are significant, in fact 3% of the budget for the Human Genome Project is allocated for the same reason. These worries range from "Brave New World-esque" fears about the beginnings of "genetic determinism" to invasions of "genetic privacy". An understandable qualm regarding predictive genetic testing is discrimination. For example, if a person is discovered to be at genetically-predisposed to developing cancer, will employers be allowed to make such individuals redundant? Will insurance companies deny claims on the same basis? In Australia, the Law Reform Commission's report details the protection of privacy, protection against unfair discrimination and maintaining ethical standards in genetics, of which the majority was accepted by the Commonwealth. [49,50] In addition, the Investment and Financial Services Association states that no applicant will be required to undergo a predictive genetic test for life insurance. [51] Undeniably, the potentially negative psychological impact of testing needs to be balanced against the benefits of detection of low, albeit significant, genetic risk. For example, population-based early detection testing for ovarian cancer is hindered by an inappropriately low positive predictive power of existing testing regimes.

As personalised medicine moves closer to becoming a reality, it raises important questions about health equality. Such discoveries are magnifying the disparity in the accessibility of cancer care for minority groups and the elderly, evidenced by their higher incidence rates and lower rates of cancer survival. This is particularly relevant in Australia, given the pre-existing pitfalls of access to medical care for Indigenous Australians. Even when calibrating for later presentations and remoteness, there have still been significant survival disparities between the Indigenous and non-Indigenous populations. [52] Therefore, a number of questions remain. Will personalised treatment serve only to exacerbate the health disparities between the developing and developed world? Even if effective personalised therapies are proven through clinical trials, how will disadvantaged populations access this care given their difficulties in accessing the services that are currently available?

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Economic Considerations

The next question that arises is: Who will pay? At first glance, stratifying patients may seem unappealing to the pharmaceutical industry, as it may mean trading the "blockbuster" drug offered to the widest possible market for a diagnostic/therapeutic drug that is highly effective but only in a specific patient cohort. Instead of drugs developed for mass use (and mass profit), drugs designed through pharmacogenomics for a niche genetic market will be exceedingly expensive. Who will cover this prohibitive cost – the patient, their private health insurer or the Government?

Training Considerations

The limiting factor in personalised medicine could be the treating doctor's familiarity with utilising genetic information. This can be addressed by enhancing genetic 'literacy' amongst doctors. The role of genetics and genetic counselling is becoming increasingly recognised, and is now a subspecialty within the Royal Australian College of Physicians. If personalised treatment improves morbidity and mortality, the proportion of cancer survivors requiring follow-up and management will also rise, and delivery of this service will fall on oncologists and general practitioners, as well as other healthcare professionals. To customise medical decisions for a cancer patient meaningfully and responsibly on the basis of the complete profile of his or her tumour genome, a physician needs to know which specific data points are clinically relevant and actionable. For example, the discovery of BRAF mutations in melanoma [32] have shown us the key first step in making this a reality, namely the creation of a clear and accessible reference of somatic mutations in all cancer types.

Downstream of this is the education that medical universities provide to their graduates in the clinical aspects of genetics. In order to maximise the application of personalised medicine it is imperative for current medical students to understand how genetic factors for cancer and drug response are determined, how they are altered by gene-gene interactions, and how to evaluate the significance of test results in the context of an individual patient with a specific medical profile. Students should acquaint themselves with the principles of genetic variation and how genome-wide studies are conducted. Importantly, we need to understand that the same principles of simple Mendelian genetics cannot be applied to the genomics of complex diseases such as cancer.

Conclusion

The importance of cancer genomics is evident in every corner of cancer research. However, its presence in the clinic is still limited. It is undeniable that much important work remains to be done in the burgeoning area of personalised therapy; from making sense of data collected from the genome-wide association studies and understanding the genetic behaviour of metastatic cancers to regulatory and economic issues. This leaves us with the parting question, are humans just a sum of their genes?

Conflicts of interest

None declared.

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Is *Chlamydia trachomatis* a cofactor for cervical cancer?

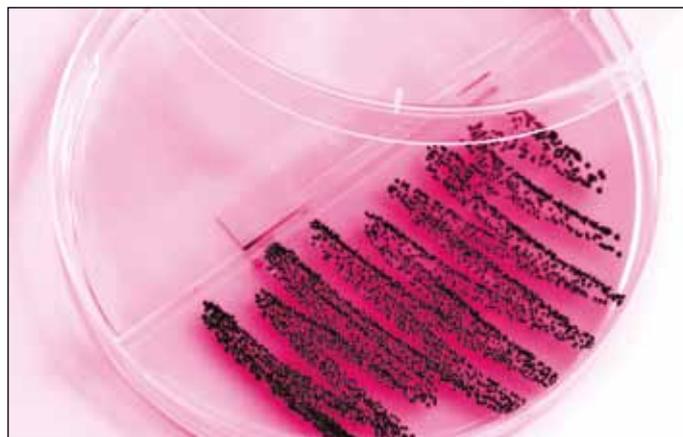
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Surabhi has a special interest in rural and indigenous health issues. She likes variety in medicine and hopes to be a 'Jack of all trades' in future. Surabhi received the Norway Bursary in year two and did a four week rotation in rural Northern Norway that helped her gain an international perspective on rural health. She is the current president of Club RHINO at JCU and also holds John Flynn and QLD rural health scholarships.

Aim: To review the literature to determine if an infection with *Chlamydia trachomatis* (CT) acts as a confounding factor in the pathogenesis of invasive cervical cancer (ICC) in women.

Methods: Web-based Medline and the Australian Institute of Health and Welfare (AIHW) search for key terms: cervical cancer (including neoplasia, malignancy and carcinoma), chlamydia, human papillomavirus (HPV) and immunology. The search was restricted to English language publications on ICC (both squamous and adenocarcinoma) and cervical intraepithelial neoplasia (CIN) between 1990-2010. **Results:** HPV is essential but not sufficient to cause ICC. Past and current infection with CT is associated with squamous cell carcinoma of the cervix of HPV-positive women. CT infection induces both protective and pathologic immune responses in the host that depend on the balance between Type-1 helper cells versus Type-2 helper cell-mediated immunity. CT most likely behaves as a cervical cancer cofactor by 1) invading the host immune system and 2) enhancing chronic inflammation. These factors increase the susceptibility of a subsequent HPV infection and build HPV persistence in the host. **Conclusion:** Prophylaxis against CT is significant in reducing the incidence of ICC in HPV-positive women. GPs should be raising awareness of the association between CT and ICC in their patients.



Evidence for the role of HPV in the aetiology and pathogenesis of cervical cancer

HPV is a species-specific, non-enveloped, double stranded DNA virus that infects squamous epithelia and consists of the major protein L1 and the minor capsid protein L2. More than 130 HPV types have been classified based on their genotype and HPV 16 (50-70% of cases) and HPV 18 (7-20% cases) are the most important players in the aetiology of cervical cancer. [6,12] Genital HPV transmission is usually spread via skin-to-skin contact during sexual intercourse but does not require vaginal or anal penetration, which implies that condoms only offer some protection against CIN and ICC. [6] The risk factors for contracting HPV infection are early age at first sexual activity, multiple sexual partners, early age at first delivery, increased number of pregnancies, smoking, immunosuppression (for example, human immunodeficiency virus or medication), and long-term oral contraceptive use. Social customs in endemic regions such as child marriages, polygamy and high parity use may also increase the likelihood of contracting HPV. [13] More than 80% of HPV infections are cleared by the host's cellular immune response, which starts about three months from the inoculation of virus. HPV can be latent for 2-12 months post-infection. [14]

Molecular Pathogenesis

HPV particles enter basal keratinocytes of mucosal epithelium via binding of virions to the basal membrane of disrupted epithelium. This is mediated via heparan surface proteoglycans (HSPGs) found in the extracellular matrix and cell surface of most cells. The virus is then internalised to establish an infection mainly via a clathrin-dependent endocytic mechanism. However, some HPV types may use alternative uptake pathways to enter cells, such as a caveolae-dependent route or the involvement of tetraspanin-enriched domains as a platform for viral uptake. [15] The virus replicates in nondividing cells that lack the necessary cellular DNA polymerases and replication factors. Therefore, HPV encodes proteins that reactivate cellular DNA synthesis in noncycling cells, inhibit apoptosis, and delay the differentiation of the infected keratinocyte, to allow viral DNA replication. [6] The integration of viral genome in the host DNA causes deregulation of E6 and E7 oncogenes of high-risk HPV (HPV 16 and 18) but not of low risk HPV (HPV 6 and 11). This results in the expression of E6 and E7 oncogenes throughout the epithelium resulting in aneuploidy and karyotypic chromosomal abnormalities that accompany keratinocyte immortalisation. [5]

Introduction

The most recent epidemiological publication on the worldwide burden of cervical cancer has reported that cervical cancer (0.53 million cases) was the third most common female cancer reported in 2008 after breast (1.38 million cases) and colorectal cancer (0.57 million cases). [1] Cervical cancer is the leading source of cancer-related death among women in Africa, Central America, South-Central Asia and Melanesia, indicating that it remains a major public health problem in spite of effective screening methods and vaccine availability. [1]

The age-standardised incidence of cervical cancer in Australian women (20-69 years) has decreased by approximately 50% from 1991 (the year the National Cervical Screening Program was introduced) to 2006 (Figure 1). [2,3] Despite this drop, the Australian Institute of Health and Welfare estimated an increase in cervical cancer incidence and mortality for 2010 by 1.5% and 9.6 % respectively. [3]

Human papillomavirus (HPV) is required but not sufficient to cause invasive cervical cancer (ICC). [4-6] Not all women with a HPV infection progress to develop ICC. This implies the existence of cofactors in the pathogenesis of ICC such as smoking, sexually transmitted infections, age at first intercourse and number of lifetime sexual partners. [7] *Chlamydia trachomatis* (CT) is the most common bacterial sexually transmitted infection (STI) and it has been associated with the development of ICC in many case-controlled and population based studies. [8-11] However, a clear cause-and effect relationship has not been elucidated between CT infection, HPV persistence and progression to ICC as an end stage. This article aims to review the literature for evidence that CT acts as a cofactor in the development of ICC and HPV establishment. The understanding of CT as a risk factor for ICC is crucial as it is amenable to prevention.

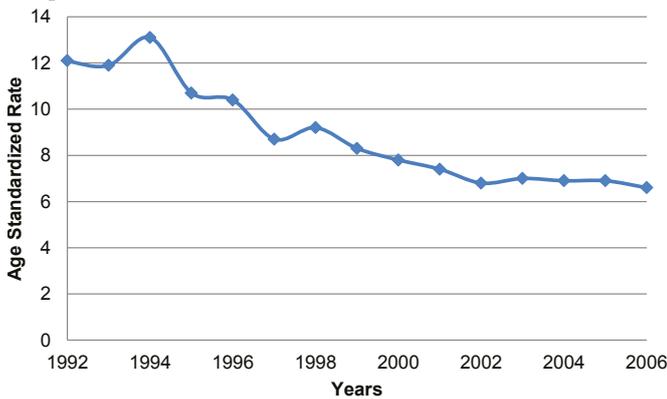


Figure 1. Incidence of cervical cancer in Australia from 1991-2006 (Adapted from AIHW, 2010). [2]

Natural History of HPV infection and cervical cancer

Low risk HPV infections are usually cleared by cellular immunity coupled with seroconversion and antibodies against major coat protein L1. [5,6,12] Infection with high-risk HPV is highly associated with the development of squamous cell and adenocarcinoma of the cervix, which is confounded by other factors such as smoking and STIs. [4,9,10] The progression of cervical cancer in response to HPV is schematically illustrated in Figure 2.

Chlamydia trachomatis and the immune response

CT is a true obligate intracellular pathogen and is the most common bacterial cause of STIs. It is associated with sexual risk-taking behaviour and leads to asymptomatic and therefore undiagnosed genital infections due to the slow growth cycle of CT. [16] A CT infection is targeted by innate immune cells, T cells and B cells. Protective immune responses control the infection whereas pathological responses lead to chronic inflammation that causes tissue damage. [17]

Innate immunity

The mucosal epithelium of the genital tract provides first line of host defence. If CT is successful in entering the mucosal epithelium, the innate immune system is activated through the recognition of pathogen-associated molecular patterns (PAMPs) such as the Toll-like receptors (TLRs). Although CT lipopolysaccharides can be recognised by TLR4, TLR2 is more crucial for signalling pro-inflammatory cytokine production. [18] This leads to the production of pro-inflammatory cytokines such as interleukin-1 (IL-1), IL-6, tumour necrosis factor- α (TNF- α) and granulocyte-macrophage colony-stimulating factor (GM-CSF). [17] In addition, chemokines such as IL-8 can increase recruitment of innate-immunity cells such as macrophages, natural killer (NK) cells, dendritic cells (DCs) and neutrophils that in turn produce more pro-inflammatory cytokines to restrict CT growth. Infected epithelial cells release matrix metalloproteases (MMPs) that contribute to tissue proteolysis and remodelling. Neutrophils also release MMPs and elastases that contribute to tissue damage. NK cells produce interferon (IFN)- γ that drives CD4 T cells toward the Th1-mediated immune response. The infected tissue is infiltrated by a mixture of CD4, CD8, B cells, and plasma cells (PCs). [17,19,20] DCs are essential for processing and presenting CT antigens to T cells and therefore linking innate and adaptive immunity.

Adaptive Immunity

Both CD4 and CD8 cells contribute to control of CT infection. In 2000, Morrison *et al.* showed that B cell-deficient mice, depleted of CD4 cells, are unable to clear CT infection. [21] However, another study in 2005 showed that passive transfer of chlamydia-specific monoclonal antibodies into B-cell deficient and CD4 depleted cells restored the ability of these mice to control a secondary CT infection. [22] This indicates a strong synergy between CD4 and B cells in the adaptive immune response to CT. B cells produce CT-specific antibodies to combat the pathogens. In contrast, CD8 cells produce IL-4, IL-5 and IL-13 that do not appear to protect against chlamydia infection and may

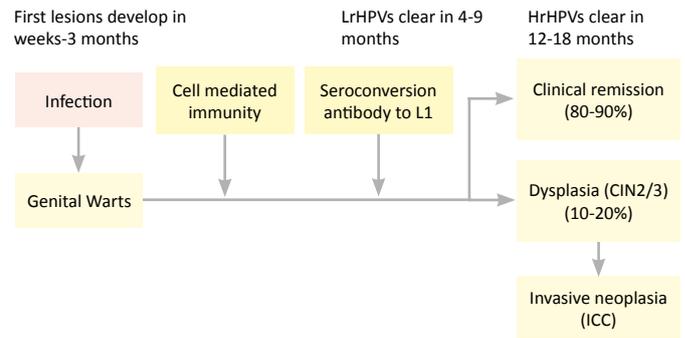


Figure 2. Steps and timeline in the development of ICC in response to HPV infection. HrHPVs: High risk HPV infection; LrHPVs: Low risk HPV infection; L1: major capsid protein.

even indirectly enhance chlamydia load by inhibiting the protective CD4 response. [23] A similar observation was made by Agrawal *et al.* who examined cervical lymphocyte cytokine responses of 255 CT antibody-positive women with or without fertility disorders (infertility and multiple spontaneous abortions) and of healthy control women negative for CT serum IgM or IgG. [20] The study revealed a significant increase in CD4 cells in the cervical mucosa of fertile women, compared with those with fertility disorders and with negative control women. There was a very small increase in CD8 cells in cervical mucosa of CT infected women in both groups. The results showed that cervical cells from the women with fertility disorders secreted higher levels of IL-1b, IL-6, IL-8, and IL-10 in response to CT; whereas, cervical cells from antibody-positive fertile women secreted significantly higher levels of IFN- γ and IL-12. This suggests that a skewed immune response toward Th1 prevalence protects against chronic infection. [20]

The pathologic response to CT can result in inflammatory damage within the upper reproductive tract due to either failed or weak Th1 action resulting in chronic infection or an exaggerated Th1 response. Alternatively, chronic infection can occur if Th2 response dominates Th1 immune response and result in autoimmunity and direct cell damage which in turn will enhance tissue inflammation. Inflammation also increases the expression of human heat shock protein (HSP), which induce production of IL-10 via autoantibodies leading to CT associated pathology such as tubal blockage and ectopic pregnancies. [24]

Evidence that Chlamydia trachomatis is a cofactor for cervical cancer

Whilst it has been established that HPV is a necessary factor in the development of cervical cancer, it is still unclear why the majority of women infected with HPV do not progress to ICC stage. Several studies in the last decade have focused on the role of STIs in the pathogenesis of ICC and discovered that CT infection is consistently associated with squamous cell ICC.

In 2000, Koskela *et al.* performed a large-scale case-controlled study within a cohort of 530,000 Nordic women to evaluate the role of CT in the development of ICC. [10] One-hundred and eighty-two women with ICC (diagnosed during a mean follow-up of five years after serum sampling) were identified via linking data files of three Nordic serum banks and the cancer registries of Finland, Norway and Sweden. Microimmunofluorescence (MIF) was used to detect CT-specific IgGs and HPV16-, 18- and 33-specific IgG antibodies were determined by standard ELISAs. Serum antibodies to CT were associated with an increased risk for cervical squamous-cell carcinoma (HPV and smoking adjusted odds ratio (OR), 2.2; 95% confidence interval (CI), 1.3-3.5). The association remained also after adjustment for smoking both in HPV16-seronegative and seropositive cases (OR, 3.0; 95% CI, 1.8-5.1; OR, 2.3, 95% CI, 0.8-7.0 respectively). This study provided sero-epidemiologic evidence that CT could cause squamous cell ICC. However the authors were unable to explain the biological association between CT and squamous cell ICC.

Many more studies emerged in 2002 to investigate this association

between CT and ICC even further. Smith *et al.* performed a hospital case-controlled study of 499 ICC women from Brazil and 539 from Manila that revealed that CT seropositive women have a two-fold increase in squamous ICC (OR, 2.1; 95% CI, 1.1-4.0) but not adenocarcinoma or adenosquamous ICC (OR, 0.8; 95% CI, 0.3-2.2). [8] Similarly, Wallin *et al.* conducted a population based prospective study of 118 women who developed cancer after having a normal pap smear (average of 5.6 years later). [25] Women were followed up for 26 years. PCR analysis for CT and HPV DNA showed that the relative risk for ICC associated with past CT, adjusted for concomitant HPV DNA positivity, was 17.1. They also concluded that the presence of CT and of HPV was not interrelated.

In contrast, another study examining the association between CT and HPV in women with cervical intraepithelial neoplasia (CIN) found that there is an increase in CT rate in HPV-positive women (29/49) as compared to HPV-negative women (10/80), ($p < 0.001$). [26] However, no correlation between HPV and CT co-infection was found and the authors suggested that the increased CT infectivity rate in HPV-positive women is presumably due to HPV-related factors, including modulation of the host's immunity. In 2004, a case-controlled study of 1,238 ICC women and 1100 control women in 7 countries coordinated by the International Agency for Research on Cancer (IARC), France also supported the findings of previous studies. [7]

Strikingly, a very recent study in 2010 confirmed that there was no association between CT infection, as assessed by DNA or IgG, and risk of cervical premalignancy, after controlling for carcinogenic HPV-positive status. [11] The authors have justified the difference in results from previous studies by criticising the retrospective nature of the IARC study, which meant that HPV and CT status at relevant times were not available. [7] However, other prospective studies have also identified the association between CT and ICC development. [9,25] Therefore, the results from this one study remain isolated from practically every other study that has found an association between CT and ICC in HPV infected women.

Consequently, it is evident that CT infection has a role in confounding squamous cell ICC in HPV infected women but it is not an independent

cause for ICC as previously suggested by Koskela *et al.* [10] Previous cause-and-effect association between CT and HPV are most likely from CT infection increasing the susceptibility to HPV. [9,11,27] The mechanisms by which CT can act as a confounder for ICC relate to CT induced inflammation (associated with metaplasia) and invasion of the host immune response, which increases susceptibility to HPV infection and enhances HPV persistence in the host. CT can directly degrade RFX-5 and USF-1 transcription factors that induce expression of MHC class I and MHC class II respectively. [17,28] This prevents recognition of both HPV and CT by CD4 and CD8 cells, thus preventing T-cell effector functions. CT can also suppress IFN-gamma-induced MHC class II expression by selective disruption of the IFN-gamma signalling pathways, hence evading host immunity. [28] Additionally, as discussed above, CT induces inflammation and metaplasia of infected cells, which predisposes them as target cells for HPV. CT infection may also increase access of HPV to the basal epithelium and increases HPV viral load. [16]

Conclusion

There is sufficient evidence to suggest that CT infection can act as a cofactor in squamous cell ICC development due to consistent positive correlations between CT infection and ICC in HPV positive women. CT invades the host immune response due to chronic inflammation and it is presumed that it prevents the clearance of HPV from the body, thereby increasing the likelihood of developing ICC. More studies are needed to establish the clear biological pathway linking CT to ICC to support the positive correlation found in epidemiological studies. An understanding of the significant role played by CT as a cofactor in ICC development should be exercised to maximise efforts in CT prophylaxis, starting at the primary health care level. Novel public health strategies must be devised to reduce CT transmission and raise awareness among women.

Conflicts of interest

None declared.

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Ovarian torsion in a 22-year old nulliparous woman

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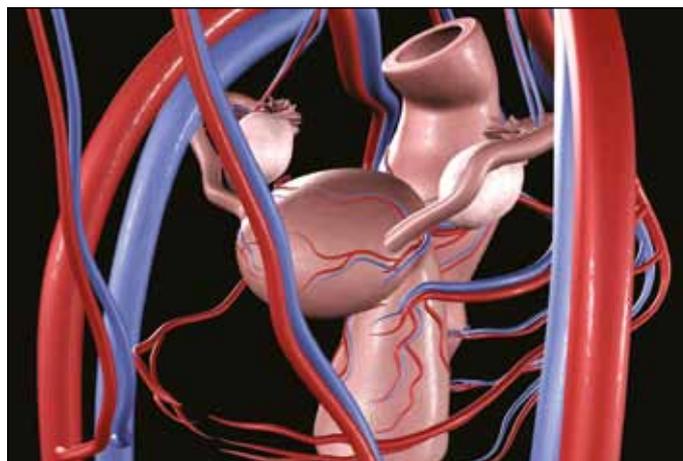
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Ovarian torsion is the fifth most common gynaecological emergency with a reported prevalence of 2.7% in all cases of acute abdominal pain. [1] It is defined as the partial or complete rotation of the adnexa around its ovarian vascular axis that may cause an interruption in the ovarian blood flow. [2] Ischaemia is therefore, a possible consequence and this may lead to subsequent necrosis of the ovary and necessitate resection. As symptoms of ovarian torsion are non-specific and variable, this condition remains a diagnostic challenge with potential implications for future fertility. [3] Consequently, clinical suspicion and timely intervention are crucial for ovarian salvage.

This case report illustrates the multiple diagnoses that may be incorrectly ascribed to the variable presentations of ovarian torsion. Furthermore, a conservative treatment approach is described in a 22-year old nulliparous woman, with the aim of preserving her fertility.



Case report

A 22 year old nulliparous woman presented to the emergency department in the middle of her regular 28 day menstrual cycle with sudden onset of right iliac fossa pain. The pain was post-coital, of a few hours duration and radiating to the back. The pain was described as constant, severe and sharp, and associated with episodes of emesis. Similar episodes of pain were experienced in the previous few weeks. These were, however, shorter in duration and resolved spontaneously. She was otherwise well and had no associated gastrointestinal or genitourinary symptoms. She had no past medical or surgical history and specifically was not using the oral contraceptive pill as a form of contraception. She was in a two year monogamous relationship, did not experience any dyspareunia and denied any prior sexually transmitted diseases. Her cervical smears were up to date and had been consistently reported as normal.

On examination, she was afebrile with a heart rate of 90 beats per minute (bpm) and a blood pressure of 126/92 mmHg. Her abdomen was described as "soft" but she displayed voluntary guarding particularly in the right iliac fossa. There was no renal angle tenderness and bowel sounds were present.

Speculum examination did not demonstrate any vaginal discharge and bimanual pelvic examination demonstrated cervical excitation with significant discomfort in the right adnexa.

Urinalysis did not suggest a urinary tract infection due to the absence of protein or blood in the urine sample. The corresponding urine pregnancy test was negative. Her blood tests confirmed the negative urine pregnancy test. There was a mild leukocytosis, and the CRP was normal.

Pelvic ultrasound demonstrated bilaterally enlarged ovaries that contained multiple echogenic masses measuring 31mm, 14.4mm, and 2mm on the right side, and 6mm, 17mm and 2mm on the left side. Blood supply to both ovaries was described as determined by blood flow Doppler. There was a small amount of free fluid in the pouch of Douglas. The report suggested there were no features suggestive of acute appendicitis and that the findings were interpreted as bilateral endometriomas. Initially her pain was unresponsive to narcotic analgesics but she was later discharged home with simple analgesics as her symptoms improved.

Two days later she represented to the hospital with an episode of post-coital vaginal bleeding and uncontrolled ongoing severe lower abdominal pain. She was now febrile with a temperature of 38.2°C and a heart rate of 92 bpm. Her blood pressure was 114/66 mmHg. Repeat blood tests revealed a slightly raised CRP of 110 mg/L and a WCC of $11.5 \times 10^9/L$. Abdominal and pelvic examinations elicited guarding and severe tenderness. On this occasion endocervical and high vaginal swabs were taken and she was treated for pelvic inflammatory disease based on her raised temperature and elevated CRP.

Subsequently, a repeated pelvic ultrasound showed bilaterally enlarged ovaries similar to the previous ultrasound. On this occasion, the ultrasound findings were interpreted as bilateral ovarian dermoids. No comment was made on ovarian blood flow, but in the right iliac fossa a tubular blind-ended, non-compressible, hyperaemic structure measuring up to 8mm in diameter was described. These latter findings were considered consistent with appendicitis.

The patient was admitted and the decision was made for an emergency laparoscopy.

Intraoperative findings revealed an 6cm diameter partially torsed left ovary containing multiple cysts, and an 8cm dark haemorrhagic oedematous torsed right ovary (Figure 1). There was a

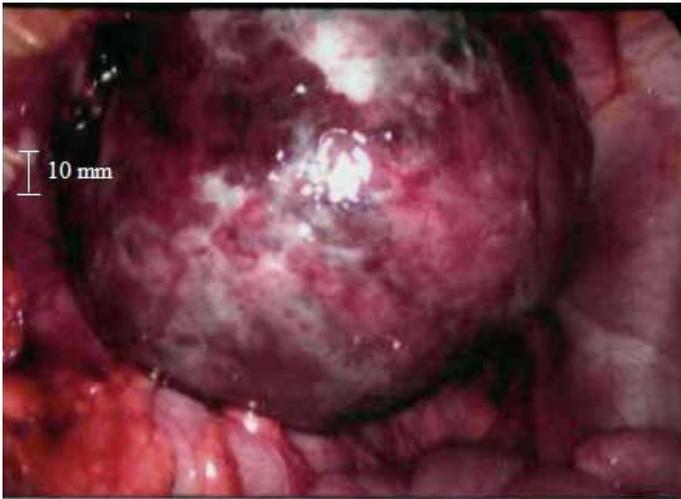


Figure 1. Laparoscopic aspect of the 8 cm dark haemorrhagic oedematous right ovary with torsion. The size of the enlarged ovary is determined by comparing to the 10 mm inserted port.

haemoperitoneum of 100 mL. Of note there was a normal appearing appendix and no evidence of adhesions, infection or endometriosis throughout the pelvis.

Laparoscopically, the right ovary was untwisted and three cystic structures, suggestive of ovarian teratomas were removed intact from the left ovary. The nature of these cystic structures was confirmed by the subsequent histopathology report of mature cystic teratomas.

During this time the colouration to the right ovary was re-established. Even though the ultrasound scan suggested cystic structures within the right ovary, due to the oedematous nature of this ovary and the haematoperitoneum that appeared to have arisen from this ovary, no attempt was made at this time to reduce the size of the ovary by cystectomy.

The postoperative period was uneventful and she was discharged home on the following day. She was well two weeks post-operation and her port sites had healed as expected. Due to the possibility of further cystic structures within her right and left ovary, a repeat pelvic ultrasound was organised in four months. The patient was reminded of her high risk of re-torsion and advised to present early if there were any further episodes of abdominal pain.

The repeat ultrasound scan confirmed the presence of two ovarian cystic structures within the left ovary measuring 3.5cm and 1.3cm in diameter as well as a 5.5cm cystic structure in the right ovary. The ultrasound scan features of these structures were consistent with ovarian dermoids. She is currently awaiting an elective laparoscopy to perform bilateral ovarian cystectomies of these dermoid structures.

Discussion

Ovarian torsion can occur at any age with the greatest incidence in women 20-30 years of age. [4] About 70% of ovarian torsion occurs on the right side, which is hypothesised to occur due the longer utero-ovarian ligament on this side. In addition, the limited space due to the presence of the sigmoid colon on the left side is also thought to contribute to the laterality incidence. [1] This is consistent with this case report in which there was partial torsion on the left side and complete torsion on the right side.

Risk factors for ovarian torsion include pregnancy, ovarian stimulation, previous abdominal surgery, and tubal ligation. [1,4] However, torsion is frequently associated with ovarian pathologies that result in enlarged ovaries. The most frequent encountered pathology is that of an ovarian dermoid, although other structures include parameso/tubal cysts, follicular cysts, endometriomas and serous/mucinous cystadenoma. [5] In this case report, despite the suggestion of endometriomas and tubo-ovarian masses secondary to presumed pelvic inflammatory

disease, bilateral ovarian dermoids were the actual cause of ovarian enlargement. The incidence of bilateral ovarian dermoids is 10-15%. [6,7]

The diagnosis of ovarian torsion is challenging as the clinical parameters yield low sensitivity and specificity. Abdominal pain is reported in the majority of patients with ovarian torsion, but the characteristics of this pain are variable. Sudden onset pain occurs in 59-87%, sharp or stabbing in 70%, and pain radiating to the flank, back or groin in 51% of patients. [4,8] Patients with incomplete torsion may present with severe pain separated by asymptomatic periods. [9] Nausea and vomiting is common in 59-85% of cases and a low grade fever in 20%. [4,8] Other non-specific symptoms including non-menstrual vaginal bleeding and leukocytosis, reported in about 4.4% and 20% of cases, respectively. [4] In this case report the patient presented with such non-specific symptoms. These symptoms are common to many other differential diagnoses of an acute abdomen, including: ectopic pregnancy, ruptured ovarian cyst, pelvic inflammatory disease, gastrointestinal infection, appendicitis, and diverticulitis. [4] In fact, the patient was initially incorrectly diagnosed as having bilateral endometriomas and together with ultrasound scan features, appendicitis was considered.

Acute appendicitis is the most common differential diagnosis in patients with ovarian torsion. Fortunately, this usually results in an operative intervention. Therefore, if a misdiagnosis has occurred, the gynaecologist is usually summoned to deal with the ovarian torsion. Conversely, gastrointestinal infection and pelvic inflammatory disease are non-surgical misdiagnoses that may result in delayed surgical intervention. [10] Consequently, it is not surprising that in one study, ovarian torsion was only considered in the admitting differential diagnosis of 19-47% of patients with actual ovarian torsion. [4] In this present case report, the patient had variable symptoms during the course of her presentations and ovarian torsion was not initially considered.

Imaging is frequently used in the management of an acute abdomen. In gynaecology, ultrasound has become the routine investigation for potential pelvic pathologies, and colour Doppler studies have been used to assess ovarian blood supply. However, the diagnostic contribution of ultrasound scan to the diagnosis of ovarian torsion remains controversial. [2] Non-specific ultrasound findings include heterogeneous ovarian stroma, "string of pearls" sign, and free fluid in the cul de sac. [2,12] However, ovarian enlargement of more than 4cm is the most consistent ultrasound feature in ovarian torsion, the greatest risk occurring in cysts measuring 8-12 cm. [2,11]

Furthermore, the use of ultrasound scan Doppler results in highly variable interpretations and some studies disagree on its usefulness. [1,2] Because cessation of venous flow precedes the interruptions in arterial flow, the presence of blood flow on ultrasound scan Doppler studies indicates probable viability of the ovary rather than the absence of ovarian torsion. [2,13] In the presented case, both ovaries demonstrated blood flow two days prior to the patient receiving an operation to de-tort her left ovary. However, it is possible that complete ovarian torsion actually occurred after the last ultrasound was performed.

Other imaging modalities, such as contrast CT and MRI, are rarely useful when the ultrasound findings are inconclusive. Thus, direct visualisation by laparoscopy or laparotomy is the gold standard to confirm the diagnosis of ovarian torsion.

Laparoscopy is the surgical approach of choice as it has the advantages of a shorter hospital stay and reduced postoperative pain requirements. [14,15] Although laparoscopy is frequently preferred in younger patients, the surgical skill in dealing with these ovarian masses may require a laparotomy. Furthermore, in patients where there is a suspicion of malignancy, for example, a raised CA125 (tumour marker) in the presence of endometriomas, a laparotomy may be appropriate. [16] Eitan *et al.* reported a 22% incidence of malignancy in 27

postmenopausal patients with adnexal torsion. [16,17]

Traditionally, radical treatment by adnexectomy was the standard approach to ovarian torsion in cases of ovarian decolouration/necrosis. This was due to the fear of pulmonary embolism from untwisting of a potentially thrombosed ovarian vein. This approach obviously resulted in the loss of the ovary and potential reduction in fertility. More recently this approach has been challenged. A more conservative treatment that consists of untwisting the adnexa followed by cystectomy or cyst aspiration has been reported. [1]

Rody *et al.* [5] suggest conservative management of ovarian torsion regardless of the macroscopic appearance of the ovary. Their large literature review reported no severe complications, such as embolism or infection, even after the detorsion of "necrotic-looking" ovaries. In support of this, animal studies suggest that reperfusion of ischaemic ovaries even after 24 hours, with a time limiting interval of 36 hours, results in ovarian viability as demonstrated histologically. [18]

This ovary sparing approach after detorsion of ischaemic ovaries is considered safe and effective in both adults and children. [19,20] A cystectomy is usually performed on suspected organic cysts for histological examination. In the case of difficult cystectomy due to ischaemic oedematous ovary, some authors recommend a re-examination 6-8 weeks following the acute episode and secondary surgery at this later time if necessary. [5,19,20] In this case report, detorsion alone of the haemorrhagic left ovary was sufficient to resolve the pain, allowing a second laparoscopic procedure to be arranged in order to remove the causative pathology.

Summary points on ovarian torsion

1. Ovarian torsion is difficult to diagnose clinically and on ultrasound.
2. Clinical suspicion of ovarian torsion determines the likelihood of

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operation.

3. Laparoscopy is the surgical approach of choice.
4. Detorsion is safe and may be preferred over excision of the torped ovary.

What did I learn from this case and my reading?

1. Accurate diagnosis of ovarian torsion is difficult.
2. Suspicion of ovarian torsion should be managed, like testicular torsion, as a surgical emergency.
3. An early laparoscopy/laparotomy should be considered in order to avoid making an inaccurate diagnosis that may significantly impact on a woman's future fertility.

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Consent declaration

Consent to publish this case report (including figure) was obtained from the patient.

Conflict of interest

None declared.

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Use of olanzapine in the treatment of acute mania: Comparison of monotherapy and combination therapy with sodium valproate

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Introduction: The aim of this article is to review the literature and outline the evidence, if any, for the effectiveness of olanzapine as a monotherapy for acute mania in comparison with the effectiveness of its use as a combined therapy with sodium valproate. **Case study:** GR, a 55 year old male with no previous psychiatric history was assessed by the Consultation and Liaison team and diagnosed with an acute manic episode. He was placed under an involuntary treatment order and was prescribed olanzapine 10mg once daily (OD). After failing to respond adequately to this treatment, sodium valproate 500mg twice daily (BD) was added to the regimen. **Methods:** A literature search was conducted using Medline Ovid and NCBI Pubmed databases. The search terms mania AND olanzapine AND valproate; acute mania AND pharmacotherapy and olanzapine AND mania were used. **Results:** Two studies were identified that addressed the efficacy and safety of olanzapine for the treatment of acute mania. Both studies confirmed the superior efficacy of olanzapine in the treatment of acute mania in comparison to placebo. There were no studies identified that directly addressed the question of whether use of combination therapy of olanzapine and sodium valproate was more efficacious than olanzapine monotherapy. **Conclusion:** There is no evidence currently available to support the use of combination olanzapine/sodium valproate as a more efficacious treatment than olanzapine alone.



and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR) criteria and placed under an involuntary treatment order. He was prescribed olanzapine 10mg OD. After failing to respond adequately to this treatment, sodium valproate 500mg BD was added to the regimen. Improvement with the addition of the new medication was seen within a number of days.

Introduction

A manic episode, as defined by the DSM-IV-TR, is characterised by a distinct period of abnormally and persistently elevated, expansive or irritable mood lasting at least one week (or any duration if hospitalisation is required) and is associated with a number of other persistent symptoms including grandiosity, decreased need for sleep, talkativeness, distractibility and psychomotor agitation, causing impaired functioning and not accounted for by another disorder. [1] Mania tends to have an acute onset and it is these episodes that define the presence of bipolar disorder. Bipolar I Disorder is characterised by mania and major depression, or mania alone, and Bipolar II Disorder is defined by hypomania and major depression. [1] The pharmacological management of acute mania involves primary treatment of the pathologically elevated mood. A number of medications are recommended including lithium, anti-epileptics either sodium valproate or carbamazepine and second generation antipsychotics such as olanzapine, quetiapine, risperidone, or ziprasidone. [2] Suggested approaches to patients with mania who fail to respond to a single medication include optimising the current drug; switching to a different drug or using drugs in combination. [2] GR was initially managed with olanzapine 10mg OD and then after failing to respond adequately, sodium valproate 500mg BD was added. This raises the following question: Is the use of combination therapy of olanzapine and sodium valproate more efficacious than olanzapine monotherapy?

Objective

The objective of this article was to review the literature and outline the evidence that is available, if any, for the effectiveness of olanzapine as a monotherapy for acute mania in comparison with the effectiveness of its use as a combined therapy with sodium valproate. The issue of long term outcome and efficacy of these two therapies is outside the scope of this particular report.

Data collection

In order to address the question identified in the objective, a literature

Case report

GR is a 55 year old Vietnamese male with no previous psychiatric history who was seen by the Consultation and Liaison Psychiatry team at a Queensland hospital after referral from the Internal Medicine team. He was brought into the Emergency Department the previous day by his ex-wife after noticing increasing bizarre behaviour and aggressiveness. He had been discharged from hospital one week earlier after bilateral knee replacement surgery twenty days prior to his current admission. GR was assessed thoroughly for delirium caused by a general medical condition, with all investigations showing normal results.

GR was previously working as an electrician, but is currently unemployed and is on a disability benefit due to a prior back injury. He currently acts as a carer for his ex-wife who resides with him at the same address. He was reported to be irritable, excessively talkative with bizarre ideas, and sleeping for less than two hours each night for the past four nights. He has no other past medical history apart from hypertension which is currently well controlled with candesartan 10mg OD. He is allergic to meloxicam with an unspecified reaction.

On assessment, GR was dressed in his nightwear, sitting on the edge of his bed. He was restless and erratic in his behaviour with little eye contact. Speech was loud, rapid and slightly pressured. Mood was unable to be established as GR did not provide a response on direct questioning. Affect was expansive, elevated and irritable. Grandiose thought was displayed with flight of ideas. There was no evidence of perceptual disturbances, in particular any hallucinations or delusions. Insight and judgement was extremely poor. GR was assessed to have a moderate risk of violence. There was no risk of suicide or self harm or risk of vulnerability.

After a request and recommendation for assessment, GR was diagnosed with an acute manic episode in accordance with Diagnostic

search was conducted using Medline Ovid and NCBI Pubmed databases with limits set to only include articles that were written in English and available as full text journals subscribed to by James Cook University. The search terms mania AND olanzapine AND valproate; acute mania AND pharmacotherapy AND olanzapine AND mania were used. A number of articles were also identified through the related articles link provided by the NCBI Pubmed Database. A number of articles including randomised controlled trials (Level II Evidence) and meta-analyses (Level I Evidence) were reviewed, however no study was found that compared the use of olanzapine as a monotherapy with the use of combined therapy of olanzapine and sodium valproate.

Discussion

Efficacy of olanzapine as a monotherapy

Two studies were identified that addressed the efficacy and safety of olanzapine for the treatment of acute mania. The first, by Tohen *et al.* in 1999 [3], was a random assignment, double blind, placebo controlled parallel group study involving a sample of 139 patients who met the DSM-IV-TR criteria for either a mixed or manic episode with 70 assigned to olanzapine 10mg OD and 69 to placebo. Both treatment groups were similar in their baseline characteristics and severity of illness with therapy lasting for three weeks. After the first day of treatment, the daily dosage could be increased or decreased by 5mg each day within the allowed range of 5-20mg/day. The use of lorazepam as a concurrent medication was allowed up to 4mg/day. [3] Patients were assessed at baseline and at the end of the study. The Young Mania Rating Scale was used as the primary efficacy measure with a change in total score from baseline to endpoint.

The study found those treated with olanzapine showed a greater mean improvement in total scores on the Young Mania Rating Scale with a difference of -5.38 points (95% CI -10.31-0.93). [3] Clinical response (decrease of 50% or more from baseline score) was also seen in 48.6% of patients receiving olanzapine compared to 24.2% of those assigned to placebo. [3] Improvement was also seen in other measures such as the severity of mania rating on the Clinical Global Impression – Bipolar version and total score on the Positive and Negative Symptom Scale. [3]

A second randomised, double blinded placebo controlled study was conducted by Tohen *et al.* in 2000. [4] This four week trial had a similar methodology with identical criteria for inclusion, primary efficacy measure and criteria for clinical response. It was, however, designed to also address some of limitations of the first trial, particularly the short treatment period, and to further determine the efficacy and safety of olanzapine in the treatment of acute mania. [4] The study design, method and assessment were clearly outlined. The study involved 115 patients and experienced a -6.65 point mean improvement in the Young Mania Rating Scale score and also showed a statistically significant greater clinical response in the olanzapine group compared to the placebo group. [4] Both studies confirmed the superior efficacy of olanzapine in the treatment of acute mania in comparison to placebo in a number of subgroups including mania versus mixed episode and psychotic-manic episode versus non-psychotic. [3,4]

The efficacy of olanzapine as monotherapy has also been compared to a number of other first line medications including lithium, haloperidol and sodium valproate. Two studies were identified that evaluated the efficacy of olanzapine and sodium valproate for the treatment of acute/mixed mania. Both demonstrated olanzapine to be an effective treatment. [5,6] Tohen *et al.* (2002) [5] showed olanzapine to have a superior improvement in mania rating scores and clinical improvement when compared to sodium valproate, however, this may have been affected by differences in dosage regimens between the study and mean model dosages. [7] Zajecka (2002) [6] described no significant differences between the two medications. In comparison to lithium, a small trial by Beck *et al.* in 1999 [8] described no statistically significant differences between the two medications. Similar rates of remission and response were shown in a twelve week double blinded study

comparing olanzapine and haloperidol for the treatment of acute mania. [9]

The evidence presented from these studies suggests olanzapine at a dosage range of 5-20mg/day is an efficacious therapy in the treatment of acute manic episodes when compared to placebo and a number of other medications.

Efficacy of combination therapy of olanzapine and sodium valproate

As mentioned previously, there was no studies identified that directly addressed the question of whether use of combination therapy of olanzapine and sodium valproate were more efficacious than olanzapine monotherapy. One study by Tohen *et al.* in 2002 [10] was identified that investigated the efficacy of olanzapine in combination with sodium valproate for the treatment of mania, however this was in comparison to sodium valproate monotherapy rather than olanzapine.

This study was a six week double-blind, placebo controlled trial that evaluated patients with failure to respond to two weeks of monotherapy with sodium valproate or lithium. 344 patients were randomised to receive either combination therapy with olanzapine or continued monotherapy with placebo. [10] Efficacy was measured by use of the Young Mania Rating Scale with results showing combination therapy with olanzapine and sodium valproate showed greater improvement in total scores as well as clinically significant improved clinical response rates when compared to sodium valproate monotherapy. [10] This improvement was demonstrated by almost all measures used in the study. However, assignment to valproate or lithium therapy was not randomized with a larger number of patients receiving valproate monotherapy. This was noted as a limitation of the study. [10] The lack of an olanzapine monotherapy group within this study also prevents exploration of a postulated synergistic effect between olanzapine and the mood stabilisers such as sodium valproate. [10]

The study by Tohen *et al.* (2002) [10] does show that olanzapine when combined with the use of sodium valproate shows superior efficacy for the treatment of manic episodes than sodium valproate alone which may indicate that combination therapy may be more effective than monotherapy. Whilst suggestive that a patient not responding to initial therapy may benefit from the addition of a second medication, these study results cannot be generalised to compare olanzapine monotherapy and sodium valproate/olanzapine combination therapy.

Conclusion

When first line monotherapy for the treatment of acute manic episodes fails, the therapeutic guidelines recommend combination therapies as an option to improve response to therapy. [2] However there is no evidence currently available to support or disprove the use of combination olanzapine/sodium valproate as a more efficacious treatment than olanzapine alone. As no studies have been conducted addressing this specific question, the ability to comment about the appropriateness of the management of GR's acute manic episode is limited.

This review has revealed a need for further studies to be undertaken evaluating the effectiveness of combination therapy for the treatment of acute manic episodes. In order to answer the question raised, it is essential that a trial be conducted with a large sample size; placebo controlled involving monotherapy with olanzapine and combination therapy in order to ascertain what approach is most effective. Another potential area for future research is for further assessment of what approach is best for those patients who fail to respond to initial monotherapy (increase current dose, change drugs or addition of medications) and then to identify whether characteristics of the patient such as whether they are experiencing a manic or mixed episode has any influence on the effectiveness of particular pharmacotherapies. This information would provide more evidence on which to base future recommendations.

There is clear evidence that supports the efficacy of olanzapine

monotherapy in the treatment of acute mania as well as evidence suggesting combined therapy with sodium valproate is also an effective treatment; however a comparison between the two approaches to management was unable to be made. When evidence is lacking, it then becomes appropriate to consider the progress of the patient in order to assess the efficacy of the current management plan, as GR experienced considerable improvement, this may indicate that his current therapy is suitable for his condition.

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Consent declaration

Informed consent was obtained from the patient for the original case report.

Conflicts of interest

None declared.

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Global inequities and the international health scene

Sir Gustav JV Nossal

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 Department of Pathology, University of Melbourne

Gustav Nossal was born in Bad Ischl, Austria, in 1931, and came to Australia with his family in 1939. He studied Medicine at The University of Sydney and, after two years' residency at Royal Prince Alfred Hospital, moved to Melbourne to work at The Walter and Eliza Hall Institute of Medical Research, where he has spent most of his research career in immunology. He has written seven books and over 530 scientific articles in this and related fields. Nossal has served as President of the Australian Academy of Science, President of the International Union of Immunological Societies, Chairman of the Victorian Health Promotion Foundation, Chairman of the committee overseeing the Global Programme for Vaccines and Immunization of the World Health Organization, Chairman of the Strategic Advisory Council of the Bill and Melinda Gates Foundation's Children's Vaccine Program and Deputy Chairman of the Council for Aboriginal Reconciliation. He was knighted in 1977, made a Companion of the Order of Australia in 1989 and has received numerous honours from 16 countries. In 2000 he was appointed Australian of the Year. He is currently Professor Emeritus, Department of Pathology, The University of Melbourne and a Principal of Foursight Associates Pty Ltd.

All young people should be deeply concerned at the global inequities that remain, and nowhere is this more clearly seen than in international health. Particularly we in the lucky country need to be mindful of this as we enjoy some of the best health standards in the world (with the notable exception of Aboriginal and Torres Strait Islander Australians). After decades of neglect, there are rays of hope emerging over the last 10-15 years. This brief essay seeks to outline the dilemma and to give some pointers to future solutions.

Mortality statistics

A stark example of the health gap is shown in Table 1, which shows that life expectancy at birth has risen markedly in the richer countries in the last 50 years, but has actually gone backwards in some countries, the situation being worst in Sub-Saharan Africa. As a result, life expectancy is now less than half of that in industrialised countries.

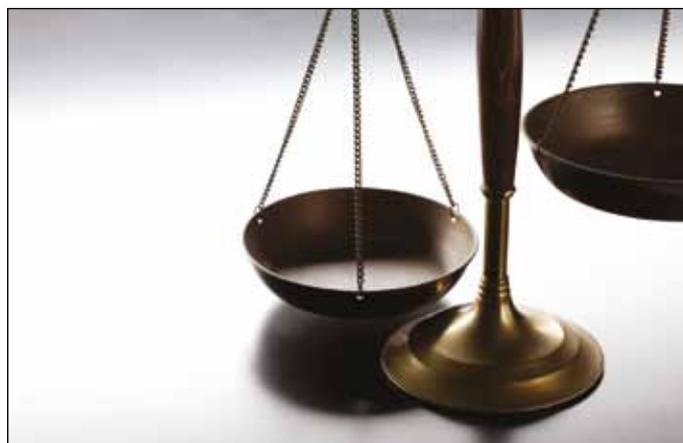
Deaths in children under five is widely used as a rough and ready measure of the health of a community, and also of the effectiveness of health services. Table 2 shows some quite exceptional reductions in the richer countries over half a century, but a bleak picture in many developing countries. India is doing reasonably well, presumably as a result of rapid economic growth, although the good effects are slow to trickle down to the rural poor. The Table shows the toll of communicable diseases and it is clear that at least two-thirds of these premature deaths are preventable.

We can total up these deaths, and note that the total comes to 20 million in 1960 and less than 8 million in 2010. Much of this improvement is due to international aid. One can do some optimistic modelling, and if we project the downward trend to 2025, deaths will be around 4.5 million. This would mean a total of 27 million extra child deaths prevented, chiefly though better treatment of pneumonia, diarrhoea and malaria; better newborn care practices; and the introduction of several new vaccines.

Table 1. Life expectancy at birth in years. [1]

Country	1960	2011
Sweden	73	81
Australia	71	82
USA	70	78
Japan	68	82
Zambia	45	39
Angola	33	38

2011 worst to best: 46%



A final chilling set of statistics is presented in Table 3. This concerns the risk of a mother dying in childbirth. As can be seen, this is now exceedingly rare in industrialised countries. With few exceptions, those rare deaths are in mothers who have some underlying serious disease not connected with their pregnancy. In contrast, deaths in childbirth are still common in poor countries. Once again, the chief causes, obstructed labour, haemorrhage and sepsis, are largely preventable. It is unconscionable that a woman is 400 times more likely to die in childbirth than in the safest country. In some villages with high birth rates and high death rates a woman's lifetime chance of dying from a pregnancy complication is one in seven!

International aid is increasing but must go higher

Properly deployed and in full partnership with the developing country, international aid can really help. At the prompting of the former Prime

Table 2. Deaths under five years per 1,000 live births. [2]

Country	1960	2011
Singapore	28.6	2.3
Japan	25.8	2.8
Australia	19.8	4.7
USA	25.4	6.3
Angola	199.9	180.2
Zambia	126.6	101.2
India	140.1	30.1
Nigeria	164.0	94.3

2009 mortality worst to best: 78%
 Last decade world improvement: 2.8% per annum
 Pneumonia 1.5 million; Diarrhoea 740,000; Malaria 670,000

Table 3. Maternal mortality per 100,000 live births. [3]

Country	1960	2011
Italy	7.4	3.9
Sweden	6.3	4.6
Australia	6.3	5.1
Japan	11.7	6.8
USA	16.6	11.5
Afghanistan	1261.0	1575.1
Sierra Leone	1044.2	1032.7
Nigeria	473.4	608.3
India	523.3	253.8

2008 mortality worst to best: 404%

Last 20 years improvement: 1.4% per annum

Minister of Canada, Lester Pearson, the United Nations mandated that the rich countries should devote 0.7% of their gross national income (GNI) to development assistance. Only five countries have reached or exceeded that goal, namely Denmark, Norway, Sweden, The Netherlands and Luxembourg. The global total is only 0.32% of GNI, or US\$128.5 billion in 2010. Australia, presently at \$4.8 billion, is pledged to go to 0.5% of GNI by 2015. The health component of aid varies from 7-15%.

Major new programmes speed progress in health

In the last 10-15 years, and for the first time, major health programmes have come forward where the budgets are measured in billions rather than millions. One with which I am particularly familiar is the GAVI Alliance, a global alliance for vaccines and immunisation. I had the honour of being involved in the "pre-history" of GAVI when I acted as the Chairman of the Strategic Advisory Council of the Bill and Melinda Gates Children's Vaccine Program from 1997-2003. Alerted to the fact that Bill and Melinda Gates wished to make a major donation in the field of vaccines a working party with representatives from the World Health Organization (WHO), UNICEF, The World Bank, and the Gates and Rockefeller Foundations engaged in a series of intense discussions with all stakeholders throughout 1998 and 1999, prominently including the Health Ministers of developing countries. GAVI was launched at the World Economic Forum in Davos in January 2000 with an initial grant of \$750 million from the Gates Foundation. Its purpose is to bring vaccines to the 72 poorest countries in the world, including newer vaccines, and to sponsor research and development of still further vaccines. As regards the six traditional childhood vaccines, namely those against diphtheria, tetanus, whooping cough, poliomyelitis, measles and BCG (for tuberculosis), 326 million additional children have been immunised and the coverage has been increased from 66% to 82%. Some 5.5 million deaths have been averted. Sturdy progress has been made in deploying vaccines against hepatitis B, one form of meningitis and yellow fever. More ambitiously, programmes are now being rolled out against pneumonia, the worst form of viral diarrhoea, cervical cancer and German measles. The budget of the GAVI Alliance is now over \$1 billion per year, but it will have to rise as further vaccines are included. There are still 19 million children unimmunised each year. One GAVI strategy is to demand some co-payment from the affected country, requiring it to give a higher priority to health and encouraging sustainability.

Two separate large programmes are addressing the problem of HIV/AIDS, arguably the worst pandemic the world has ever faced. They are the Global Fund for AIDS, TB and Malaria and PEPFAR, the US President's Emergency Fund for AIDS Relief. Together these programmes spend an astonishing US\$12 billion per year. As a result, highly active antiviral therapy (HAART) is reaching 6.5 million people in low and middle income countries, not only prolonging their lives indefinitely but also lowering the virus load in their blood, thus diminishing their capacity to transmit the virus. There is good evidence that the epidemic has

peaked with the number of new cases going down each year. In addition, special effort is going into the prevention of mother to child transmission of HIV.

The search for an AIDS vaccine continues. An encouraging but vexing result emerged from a clinical trial of Sanofi-Pasteur's vaccine in Thailand, involving 16,000 volunteers. The vaccine gave 31.2% protection from HIV infection, clearly not sufficient to go forward with mass immunisation, but enough to warrant further investigation in what has previously been a rather discouraging field.

Progress in malaria has been substantial. Insecticide-impregnated bednets turn out to be a powerful weapon, causing a 5% lowering of mortality where they are used. The Global Fund has distributed 240 million of these, and it is planned to reach a total of 700 million, an astonishing effort. Chemotherapy has been increased, including IPT, intermittent preventive therapy, where a whole population of children receives antimalarials every six months. IPT is also useful in pregnant women. A malaria vaccine is in the late phases of clinical trial. Produced by GlaxoSmithKline, it is known as RTS,S and has proven about 50% effective. It is targeted at the surface of that life-form of the parasite, known as sporozoite, which leaves the mosquito's salivary gland and is injected under the skin when the mosquito feeds. Most experts believe that the final, definitive malaria vaccine will also need to target the liver cell stage, where the parasite goes underground, the blood cell stage, where it multiplies extensively in red blood cells, and perhaps the sexual stages. Good progress is being made in research in all these areas.

Tuberculosis remains a formidable foe particularly as resistance to anti-tuberculous drugs is developing. That being said, the Global Fund is treating 8.7 million tuberculosis patients with DOTS (directly-observed therapy, short term, to assure compliance). Sadly, short term means six months, which is quite a burden. Extensive research is seeking newer drugs able to act in a shorter time frame. As regards vaccines, unfortunately it is clear that the birth dose of BCG, which does a good job of preventing the infant manifestations of TB, namely tuberculous meningitis and widespread miliary tuberculosis, is ineffective in preventing the much more common pulmonary tuberculosis of adolescents and young adults. An impressive body of research is attempting to develop new TB vaccines. Three are in Phase II clinical trial and at least eight in Phase I trial. The chronic nature of tuberculosis makes this a slow and expensive exercise.

The challenge of global eradication of poliomyelitis

Following the triumph of global eradication of smallpox, WHO set itself the challenge of eradicating poliomyelitis. When I was young, this was a most feared disease, with its capacity to kill and maim. The Salk vaccine and then later the oral Sabin live attenuated vaccine brought the disease under control in the industrialised countries with remarkable speed. A dedicated effort in Latin America did the same. But in Africa and the Indian subcontinent it was a different story. For this reason, a major partnership was launched in 1988 between the voluntary organisation Rotary International, WHO and UNICEF, with help from many others, to eradicate polio globally. Five strategies underpinned the venture. The Sabin oral polio vaccine was used to cut costs and ease administration, as oral drops rather than an injection was needed. High routine infant immunisation rates were encouraged. To get to the hard to reach children, national immunisation days were instituted, where all children under five were lined up and given the drops, regardless of previous immunisation history. Strong emphasis was placed on surveillance of all cases of paralysis with laboratory confirmation of suspected cases.

Finally, as control approached, a big effort was made to quell every little outbreak, with two extra doses of vaccine two weeks apart around the index case. As a result of this work, polio cases were reduced by over 99%. In 2011, there were only 650 confirmed cases in the whole world. India deserves special praise. Despite the large population and widespread poverty, the last case in India occurred on

13 January, 2011. There are now only three countries in which polio has never been eradicated, namely Pakistan, Afghanistan and Nigeria. Unfortunately, three countries have re-established polio transmission after prior eradication: Chad, DR Congo and Angola. Furthermore, sporadic cases are occurring in other countries following importation, though most of those mini-outbreaks are quickly controlled. We are at a pivotal point in this campaign. It is costing about \$1 billion per year to maintain the whole global apparatus while the public health

burden is currently quite small. Cessation of transmission was targeted for end 2012; this deadline is unlikely to be met. But failure to reach the end goal would constitute the most expensive public health failure in history. If we can get there, the economic benefits of eradication have been estimated at US\$40-50 billion.

Some further vaccine challenges are listed in Table 4. In a twenty year framework success in most of these is not unrealistic. The dividends would be enormous; finding the requisite funds will be a daunting task.

Table 4. Some further vaccine challenges.

Type	Challenges
Bacterial	<ul style="list-style-type: none"> • Protein for meningococcus B • Protein for pneumococcus • Various approaches for Group A streptococcus • Vi-conjugate for <i>Salmonella typhi</i> • Live attenuated or subunit vaccines for <i>Shigella</i> • Live attenuated or subunit vaccines for <i>Helicobacter pylori</i>
Viral	<ul style="list-style-type: none"> • Dengue (Sanofi Pasteur Phase III end 2012) • Cheaper rotavirus – India prominent (Bharat, Shanta, Serum Institute of India) • Broadly active influenza • Inhalable measles
Parasitic	<ul style="list-style-type: none"> • More complete malaria vaccine (liver, blood, sexual stage antigens) • Protozoa: leishmaniasis, trypanosomiasis • Metazoa: schistosomiasis, hookworm, onchocerciasis, <i>Taenia</i>

Conclusions

This essay focuses on infections and vaccines, my own area of expertise, but plentiful pathways for progress exist in other areas. New drugs for all the above diseases; clever biological methods of vector control; improved staple crops with higher micronutrients and protein through genetic technologies; stratagems for improved antenatal care and obstetrics; a wider array of contraceptive measures tailored to particular cultures; in time thrusting approaches to non-communicable diseases including cardiovascular disease, diabetes, obesity, hypertension and their consequences; and greater recognition of the importance of mental health with depression looming as a very grave problem. As young people contemplating a career in medicine, I commend all of these areas to you. In particular, consider spending some months or a few years in joining this battle to provide better health to all the world's citizens. There are plenty of opportunities and the relevant travel will certainly prove enriching. A new breeze is blowing through global health. The thought that we can build a better world has taken firm hold. It is your generation, dear readers, who can turn dreams into realities and make the twenty-first century one truly to remember.

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The role of medical students in innovation

Prof Fiona Wood

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Professor Fiona Wood is a plastic surgeon and Director of Burn Services of Western Australia. She works at Royal Perth Hospital and Princess Margaret Hospital for Children. She is the Chair and co-founder of the McComb Research Foundation, which she established in 1999 along with scientist Marie Stoner. Fiona's research through the McComb Research Foundation involves collaborative projects dedicated to research and education into burns, trauma and scarless healing. Fiona was awarded the Australian Medical Association "Contribution to Medicine" Award, in 2003 and also received the Order of Australia Medal for work with Bali bombing victims. She was named West Australian of the Year for 2004, and was nominated as a National Living Treasure and Australian Citizen of the Year in 2004. In 2005 she received the honour of being named Australian of the Year.

When thinking about the role of medical students in innovation, my mind drifts back to my early days in St Thomas' Hospital Medical School, London 1975. It was exciting because I could see for the first time that I had a role in the world that was useful. Let's face it, until then it is pretty well a one-way street, with education being handed to us and us taking it; but here, I could see a chance to grow and to contribute in a way I had not been able to do so. Then came the big question: How?

My "research career" started early: I knew that I needed a CV that was interesting to get a sniff of a surgical job, so not all out of pure curiosity. My Bachelor of Medical Science equivalent was both interesting and frustrating, but most importantly, it taught me that I could question. More to the point, that I could work out the strategies to answer the questions. Exploring the evolution of the brain from worms to elephants was fascinating, but did I find the point where the central nervous system (CNS) and peripheral nervous system (PNS) transitioned? No! But I did get to go on an anthropology field trip to Kenya and Tanzania and work collecting fossils on the Leaky camp, which was a huge bonus.

So, when I got to my Obstetrics and Gynaecology term, I decided that India was a good place to investigate malnutrition in pregnancy. Looking back, I find it hard to figure how I put the trip together with the funding and the equipment. But a long shaggy dog story short, my friend Jenny and I tripped off to a government hospital and measured anthropometric measurements, HbA_{1c} as a measure of carbohydrate metabolism, and RBP, a protein with a high essential amino acid content, to measure the protein metabolism (measured on gel plates by yours truly as I got back). It was a great trip, a huge learning on lots of levels and it still remains with me.

Having submitted the work to the British Journal of Nutrition, it was sent back for revisions. However, I didn't have the understanding to realise that was good and that I just needed to revise and send my changes back. Instead, totally deflated I put it in a file and tried hard to forget that I had failed at the last fence. I clearly was never successful in forgetting! Finishing is key, otherwise you have used resources, yours and others', and selfishly not added to the body of knowledge. Sounds harsh, but even negatives should be published: How many resources are wasted in repetition? Finishing is essential for all of us. Anyone can start, but learn the value of *finishing* - I learnt early and it is with me still.

I will fast forward a little to the early days of my surgical training, when I saw amazing things being done by the plastic surgeons, and I was hooked. At the time, microsurgery was gaining momentum, tissue expansion was being explored, and tissue culture for clinical skin replacement were all in the mix. Yes, heady times indeed! One surgeon told me, "Medicine is 5% fact. The rest, well, opinion based on experience. The aim is to find the facts, hold on to them, and build the body of evidence." Someone else once told me, "Believe nothing of what you hear and only half of what you see!"



Regarding tissue expansion, it was said casually by my consultant that, "It's all well and good to create skin with characteristics similar to the defect, but the nerves are static and so the quality of innervation will decrease as the skin is expanded." Really? I wasn't so sure. So, off to find a friendly neurophysiologist who helped me design an experiment, and taught me how to do single axon recordings on T11 of a rodent model. We proved for the first time that the peripheral nerve field was not static but responded to the changes in the skin with forces applied.

We are now familiar with neural plasticity. Understanding CNS and PNS plasticity remains a corner stone of my research efforts exploring the role in healing the skin. How do we harness the capacity to self organise back to our skin shape, not scar shape, on a microscopic level? How can we think ourselves whole? Questions that stretch and challenge us are always the best ones!

The spray on skin cell story for me started in 1985 in Queen Victoria Hospital, East Grinstead, when I saw scientists growing skin cells. Another wow moment. So, I read all I could get my hands on. That is the starting point, to know what is out there. There is no point in re-inventing the wheel! In 1990, as a Registrar in Perth, with the help of the team in Monash, Professor John Masterton and Joanne Paddle, our first patient was treated in Western Australia. By 1993, Marie Stoner and I had a lab in Perth funded by Telethon, exploring the time taken to expand the number of a patient's skin cells to heal the wounds as rapidly as possible. By 1995, we were delivering in a spray instead of sheets. We then developed a kit to harvest cells for bedside use, using

the wound as the tissue culture environment. This is now in clinical trials around the world, some funded by the US Armed Forces Institute of Regenerative Medicine. That is another lesson: The work never stops, it simply evolves.

So, asking questions is the starting point. Then, finding out how to answer the question, who can help support, do some work, fund it, etc., are all valid questions. BUT you must also ask, what direction do you go when there are so many questions? Go in the direction that interests you. Follow your passion. Not got one? Then expose yourself

to clinical problems until you meet a patient you want to help like no other, in a subject area that gets you out of bed in the morning. Then, you will finish, maybe not with the answer, but with a contribution to the body of knowledge such that we all benefit.

Do medical students have a role? A group of highly competitive intellectual problem-solvers? Absolutely, if they choose to. I would say start now, link with positive energy, keep your ears and eyes open, and always learn from today to make sure tomorrow is better, and that we pass on medical knowledge and systems we are proud of.

NSW PUBLIC HEALTH BULLETIN

Immunisation in NSW

NSW immunisation performance: continuing progress but no room for complacency

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Complacency is the greatest threat to successful immunisation programs. This has recently been demonstrated in many countries in Europe with resurgence of vaccine preventable diseases that were previously well controlled, particularly measles.¹ Thus in New South Wales (NSW), despite having a successful immunisation program, we must continue to review performance carefully, identify signals of complacency and strive to protect vulnerable members of our community with the wide range of vaccines that we have at our disposal.

This issue of the *NSW Public Health Bulletin* presents the second in a series of annual reports which provide a comprehensive overview of the current epidemiology of vaccine-preventable diseases in NSW and the status of our immunisation program. 2010 was the third year of NSW's second immunisation strategy (in place from 2008 to 2011)² and saw further progress in a number of areas such as vaccine coverage and timeliness. Changes in vaccine recommendations, the ongoing pertussis challenge and the adverse events associated with seasonal influenza vaccine use in young children, are some of the features highlighted.

In the *NSW Annual Vaccine Preventable Disease Report, 2010*, by Spokes and Gilmour, it is gratifying to see that most notifiable vaccine preventable diseases in NSW remain under good control. For example, cases of *Haemophilus influenzae* serotype B (Hib), meningococcal C and pneumococcal disease remain at low levels. Although rates of invasive pneumococcal disease are still highest in children below 5 years of age, almost all strains (94%) identified in cases were those not covered by the 7-valent conjugate pneumococcal vaccine (7vPCV). The introduction of a

13-valent PCV nationally in 2011, to replace the 7-valent vaccine, holds promise for further decline in disease incidence due to the additional six vaccine serotypes.

The ongoing pertussis epidemic poses important challenges.³ 2010 saw changes in the epidemiology of the disease; notification rates decreased in children under 4 years of age (although these rates continue to be high) and increased in the 5–14-year age group. As seen in the Annual Coverage report by Hull et al, two high school-based cohorts of adolescents were provided with the adult and adolescent formulation of the diphtheria, tetanus and acellular pertussis-containing (dTpa) vaccine in 2010 (year 7 and year 10). This immunisation program aimed to increase and bring forward protection for adolescents, in whom immunity may be waning after the fourth booster dose (at 4 years of age). It was reassuring to see a more than 50% decline in notification rates among infants below 12 months of age. Earlier receipt of the first dose of pertussis-containing vaccine for infants (at 6 weeks rather than 2 months of age) has been recommended in NSW since 2009 in response to the current epidemic.⁴ As reported by Hull et al, this earlier schedule has resulted in a large increase in the proportion of babies (over 60%) receiving the first dose before 8 weeks of age and thus being afforded at least partial protection against severe disease. Another strategy has been the provision of free vaccine to the parents and carers of young infants, funded in NSW as the 'cocoon program'.⁴ This strategy is currently being formally evaluated for its impact on infant disease which should inform ongoing policy in this area. Clearly the focus of pertussis vaccination efforts must remain on preventing disease in those most vulnerable to severe morbidity and mortality – infants, especially those below 6 months of age.

Cases of measles, often introduced by young unimmunised Australians returning from travel overseas to measles endemic areas, or visitors from these areas, led to sporadic outbreaks of the disease across NSW in 2010, particularly in those aged 10–19 years. Index cases (the first to contract disease in an outbreak) often passed

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Addressing common legal and ethical concerns with off-label prescribing in Australia

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Introduction

Off-label (unapproved, or unlabelled) prescribing refers to the supply of a medication for an indication, age, dosage or route of administration that is not included in approved product information or registration. [1] Such practice is widespread, occurring at rates of up to 40% in adults and up to 90% in paediatric patients. [2] In some cases, off-label prescribing may be supported by current, high-quality scientific evidence, which has emerged subsequent to publication of approved product information. While Australian data in this area is lacking, data from the USA shows the majority of off-label prescriptions are not evidence-based, with 73% of a surveyed 150 million off-label prescriptions lacking scientific evidence to support their use. [2] This raises a number of legal and ethical issues for both prescribers and patients.

What is the legal status of off-label prescribing?

In a survey of 327 general practitioners, 53% stated they did not know, or gave the wrong answer, when asked about the legal status of off-label prescribing. [1] While it is reasonable to expect the incidence of off-label use to be greater in a specialist setting, comparative data with general practice is lacking. Given the estimated overall high incidence of off-label prescribing, an understanding of its legal status is important for both GPs and specialists.

In the ACT, prescription drugs are controlled under the Medicines, Poisons, and Therapeutic Goods Act 2008 (ACT), which states that a health professional who prescribes a medicine must ensure the supply is for a quantity and purpose consistent with the recognised therapeutic standard appropriate in the circumstances (ch.2, s.7). [3] What is “appropriate in the circumstances” will differ between cases and is decided by the medical practitioner. Nonetheless, prescribing decisions should arguably have an evidence base in order to comply with the Act.

The chief body responsible for regulating pharmaceutical products in Australia, the Therapeutic Goods Administration (TGA), does not regulate the prescription or administration of medicines once they are registered under the Therapeutic Goods Act 1989 and have entered the market. [4] Therefore, off-label prescribing is legal. This was noted in the case of Commonwealth of Australia v Human Rights & Equal Opportunity Commission (1997) 147 ALR 469, which found that off-label prescribing of medicines registered under the Therapeutic Goods Act 1989 would not appear in breach of the Act provided the prescription or administration was not authorised or performed by a sponsor of the medicine. [5] Thus medical practitioners may prescribe approved drugs for any purpose they believe will benefit their patients regardless of the approved terms of use registered by the TGA.

Is off-label prescribing a deviation of the standard of care? Is it litigiously risky?

Off-label prescribing carries the same medicolegal obligations as on-label prescribing. The standard of care remains unchanged. The medical practitioner has a duty to, among other things, inform their patient of all material risks inherent in the proposed treatment as well as those of alternative treatments (see *Rogers v Whitaker* (1992) 175 CLR 479). If sued for negligence, the practitioner will be judged according to the reasonable nature of their actions in the given



circumstances (in ACT see Civil Law (Wrongs) Act 2002 (ACT)) or by the reasonable body of medical opinion (in NSW see Civil Liability Act 2002 (NSW), encompassing the ratio decidendi of *Bolam v Friern Hospital Management Committee* (1957) 1 WLR 582).

For a medical practitioner to be found negligent, the patient must demonstrate to the Court that, on the balance of probabilities, the practitioner had a duty of care to the patient, which they breached, directly causing harm to the patient. The off-label status of a drug does not alter these essential elements of negligence, and cannot be used alone as evidence of negligence. An exception to this may exist where a manufacturer clearly warns against a specific off-label use. This was illustrated in the case of *Richardson v. Miller* 2000 44 S.W.3d 1 (USA) where evidence regarding the off-label use of terbutaline for tocolysis was excluded from the trial because it did not indicate a deviation of the standard of care. This exclusion was, however, reversed at appeal, as the manufacturer explicitly warned against the use of terbutaline for this purpose.

Failure to treat with an off-label drug may also expose practitioners to litigation. Where it becomes standard best practice to administer a drug for an unapproved indication, failure to do so, may be a breach of the duty of care. This is exemplified in paediatric medicine, as the majority (>70%) of registered drugs are not approved for use in children. [6] This is not surprising as it is challenging for drug sponsors to obtain the necessary clinical trial data to support their application for a paediatric indication. The ongoing paediatric exclusivity provisions enacted by the FDA in 1997 aimed to address this issue by providing sponsors with additional patent protection in return for conducting paediatric studies. [7]

In many instances off-label use in children represents the current standard of care, and withholding essential treatment, due to fears of off-label prescribing, would be negligent. [8] This highlights the importance of continuing professional education. Practitioners must remain up-to-date with current clinical evidence to ensure they meet their standard of care.

Perhaps the litmus test for avoiding medical liability in this area is the foremost consideration of the best interests of the patient. [9] Whether prescribing on- or off-label, proposed treatments should be based on scientific and clinical data, with costs, benefits, and alternatives thoroughly explained to patients before gaining consent.

Should doctors inform patients that they are prescribing them a treatment that is off-label?

There are conflicting views around this issue in the medical and legal literature. Some argue that the safety, efficacy, and adverse effects of drugs prescribed off-label are unknown and knowledge of this fact may influence patient's decisions to accept or reject treatment. In this respect knowledge of off-label status may be considered a "material risk" that patients should be informed about. Conversely, some argue that patients may erroneously associate lack of TGA approval with TGA disapproval, and instinctively refuse effective treatment. [10] This latter view reflects an out-dated paternalistic notion that patients are incapable of acting in their own best interest and that practitioners should employ Therapeutic Privilege to protect patients from themselves.

Where the off-label use of a particular drug is best practice and/or supported by quality evidence there may be less onus on the practitioner to inform the patient of a drug's off-label status. However, patients understandably become confused and frustrated when, for example, they are prescribed amitriptyline for neuropathic pain only to read in the enclosed consumer medicines information (CMI) brochure that it is indicated for depression and nocturnal enuresis. [5] This confusion may undermine the therapeutic doctor-patient relationship.

The principle of informed consent promotes patient autonomy and self-determination and acknowledges the central position of the patient in clinical decision-making. Whether knowledge of a drug's off-label status is considered a material risk is yet to be tested in an Australia court, however, in most circumstances, practitioners would be wise to err on the side of caution and inform patients.

Is the promotion of drugs for off-label indications by drug sponsors unethical?

Advertising medicines to practitioners for unapproved indications is both unethical and illegal in Australia. Section two of the Medicines Australia Code of Conduct states that "*the content of all promotional material provided to health professional must be... fully supported by the Product Information.*" [11] Adherence to this code is mandatory for all drug sponsors, regardless of their membership with Medicines Australia.

The TGA approval process is expensive, rigorous, and time consuming, but serves an essential role in public protection and safety. Allowing companies to market drugs for off-label purposes removes the incentive to conduct clinical research to prove the safety and efficacy of their products. [12] Pharmaceutical companies have a vested interest in promoting the untested and unapproved use of their products. It is financially advantageous to alter prescribing patterns in favour of their product. This may corrupt the therapeutic doctor-patient relationship through the promotion of inappropriate, untested, and potentially unsafe drugs.

The withdrawal of fenfluramine and dexfenfluramine by American Home Products (AHP) from the USA market in 1997, and subsequent class action suit, illustrates the dangers of promoting off-label prescribing. [13] These drugs were initially approved as short-term, standalone weight loss drugs, however in 1992 preliminary evidence emerged suggesting an advantageous combination with another weight loss drug, phentermine (the so dubbed Fen-Phen combination). While both drugs had independent approval from the Food and Drug Administration (FDA), their combination was not approved. Moreover, AHP representatives responded to practitioner enquires by providing research papers, effectively endorsing the off-label combination. [14] In 1997 reports surfaced indicating an increased incidence of pulmonary hypertension and valvular heart disease among those using the Fen-Phen combination. The ensuing case settled for an estimated \$16 billion. [14] This case highlights, among other things, the potentially devastating consequences of off-label drug promotion. Such behaviour by pharmaceutical companies bypasses the strict

review processes of regulatory bodies (such as the TGA) compromising consumer protection and safety. [15]

More recently, a phenomenal rise in off-label prescriptions for gabapentin (an anticonvulsant) in the USA has been, at least partially, attributed to the illegal marketing practices of pharmaceutical company Warner-Lambert. [16] In 2004, Warner-Lambert was fined \$430 million for suppressing negative clinical trials and promoting the off-label use of gabapentin for migraine, bipolar disorder, and neuropathic pain despite having little or no supporting clinical evidence at the time. [17] Using deceptive means to persuade doctors to prescribe costly, unproven, and potentially ineffective drugs is clearly unethical, and ultimately subverts patient health for corporate gains. Prescribers are encouraged to report any unethical behaviour of pharmaceutical representatives to Medicines Australia. [18]

Is the off-label use of drugs a form of human research/experimentation?

The intention of the prescriber determines whether the use of a drug is classified as "therapy" or "experimentation". As outlined in the Belmont Report (1979), clinical practice involves treating a patient with the sole aim of improving their wellbeing. [19] This is distinct from research (or experimentation), which principally aims to test a hypothesis, draw conclusions, gain knowledge and understanding, or to train researchers. [19,20] Research on human subjects must be ethically justifiable – it must have merit, and its researches must have integrity. [20] Additionally, human research is governed by Australian law, imposing responsibilities on investigators and protecting the rights of participants. [20]

Off-label prescribing often blurs the boundary between practice and research, and indeed both may occur simultaneously. Where little or no clinical data is available to guide off-label therapy, practitioners may prescribe drugs with the intention of improving patient wellbeing, but also with the intention of publishing treatment outcomes to provide anecdotal evidence for future prescribers. Such case reports may identify effective new applications of existing drugs, and pave the way for clinical studies.

Lawrence Craven, an American general practitioner, first noted the antithrombotic effects of aspirin in 1950 after observing increased bleeding rates among those who chewed aspirin gum following dental surgery. [21] He soon began prescribing the drug off-label to his patients to prevent myocardial infarction. While his published findings were ignored at the time, they were later supported by large scale clinical trials, eventually leading to the widespread acceptance and approval of aspirin for cardiovascular protection in the 1990s. [21,22] Craven's off-label use of aspirin arguably blurred the line between research and therapy but ultimately flagged an important avenue for further clinical research, and had his findings been appreciated at the time, they may have saved many lives.

When should doctors prescribe drugs off-label?

Off-label use is appropriate when the potential benefits of treatment are deemed to exceed the potential risks in a given clinical context. This will involve a systematic consideration of both the available evidence for safety and efficacy and the seriousness of the condition being treated. [5] In some instances quality evidence supporting use in a particular indication will be lacking, and extensive clinical experience ("expert opinion") may be relied upon. The quantity and quality of evidence required for a favourable risk-benefit ratio will logically be less with more serious diagnoses. Where the TGA has not rigorously assessed a drug for a particular use, the onus is on the practitioner to do so. If they believe a favourable risk benefit ratio exists, they may prescribe treatment once informed consent has been obtained.

In the absence of supporting evidence or expert opinion, off-label use is generally not justified, except when used in the context of formal, approved research, or in exceptional cases with compelling individual

circumstances. [2,5] Such individual circumstances typically involve severe disease refractory to standard treatment. In these cases, there must be some evidence to support the proposed treatment as well as a favourable risk benefit ratio, and approval by an institutional drug committee. [2]

Increasingly, practitioners must consider drug cost when prescribing off-label. For drugs requiring authority approval, the Pharmaceutical Benefits Scheme (PBS) provides subsidised medicines for approved indications only. With the influx of expensive biological agents with narrow listings on the PBS, supply outside of approved indications may incur a high price. It is worth noting that most off-label use currently involves relatively inexpensive drugs for which cost would influence little on the prescribing decision.

Conclusion

Off-label prescribing is both legal and necessary. The TGA approval process lags substantially behind the rapidly emerging clinical evidence supporting novel uses of existing drugs. The clinical data required by the TGA for an extension of indication is difficult and expensive for drug

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sponsors to obtain, especially in paediatric populations. Lack of TGA approval does not equate to TGA disapproval and in many cases the use of drugs outside of their approved product listing represents the current standard of care. Failure to provide such drugs may constitute medical negligence, and practitioners should remain up-to-date with current clinical evidence to ensure they meet their standard of care. When off-label prescribing is supported by quality scientific evidence and is likely to improve patient wellbeing, it is ethically justified and should be offered to patients.

Disclaimer

The above commentary is not intended to be legal advice and should not be relied upon as such.

Conflicts of interest

None declared.

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The ethics of euthanasia

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Introduction

The topic of euthanasia is one that is shrouded with much ethical debate and ambiguity. Various types of euthanasia are recognised, with active voluntary euthanasia, assisted suicide and physician-assisted suicide eliciting the most controversy. [1] Broadly speaking, these terms are used to describe the termination of a person’s life to end their suffering, usually through the administration of drugs.

Euthanasia is currently illegal in all Australian states, reflecting the status quo of most countries, although, there are a handful of countries and states where acts of euthanasia are legally permitted under certain conditions.

Advocates of euthanasia argue that people have a right to make their own decisions regarding death, and that euthanasia is intended to alleviate pain and suffering, hence being ascribed the term “mercy killing.” They hold the view that active euthanasia is not morally worse than the withdrawal or withholding of medical treatment, and erroneously describe this practice as “passive euthanasia.” Such views are contested by opponents of euthanasia who raise the argument of the sanctity of human life and that euthanasia is equal to murder, and moreover, abuses autonomy and human rights. Furthermore, it is said that good palliative care can provide relief from suffering to patients and unlike euthanasia, should be the answer in modern medicine.

This article will define several terms relating to euthanasia in order to frame the key arguments used by proponents and opponents of euthanasia. It will also outline the legal situation of euthanasia in Australia and countries abroad.

Defining euthanasia

The term “euthanasia” is derived from Greek, literally meaning “good death”. [1] Taken in its common usage however, euthanasia refers to the termination of a person’s life, to end their suffering, usually from an incurable or terminal condition. [1] It is for this reason that euthanasia was also coined the name “mercy killing”.

Various types of euthanasia are recognised. Active euthanasia refers to the deliberate act, usually through the intentional administration of lethal drugs, to end an incurably or terminally ill patient’s life. [2] On the other hand, supporters of euthanasia use another term, “passive euthanasia” to describe the deliberate withholding or withdrawal of life-prolonging medical treatment resulting in the patient’s death. [2] Unsurprisingly, the term “passive euthanasia” has been described as a misnomer. In Australia and most countries around the world, this practice is not considered as euthanasia at all. Indeed, according to Bartels and Otlowski [2] withholding or withdrawing life-prolonging treatment, either at the request of the patient or when it is considered to be in the best interests of the patient, “has become an established part of medical practice and is relatively uncontroversial.”

Acts of euthanasia are further categorised as “voluntary”, “involuntary” and “non-voluntary.” Voluntary euthanasia refers to euthanasia performed at the request of the patient. [1] Involuntary euthanasia is the term used to describe the situation where euthanasia is performed when the patient does not request it, with the intent of relieving their suffering – which, in effect, amounts to murder. [3] Non-voluntary euthanasia relates to a situation where euthanasia is performed when the patient is incapable of consenting. [1] The term that is relevant to the euthanasia debate is “active voluntary euthanasia”, which



collectively refers to the deliberate act to end an incurable or terminally ill patient’s life, usually through the administration of lethal drugs at his or her request.

The main difference between active voluntary euthanasia and assisted suicide is that in assisted suicide and physician-assisted suicide, the patient performs the killing act. [2] Assisted suicide is when a person intentionally assists a patient, at their request, to terminate his or her life. [2] Physician-assisted suicide refers to a situation where a physician intentionally assists a patient, at their request, to end his or her life, for example, by the provision of information and drugs. [3]

Another concept that is linked to end-of-life decisions and should be differentiated from euthanasia is the doctrine of double effect. The doctrine of double effect excuses the death of the patient that may result, as a secondary effect, from an action taken with the primary intention of alleviating pain. [4] Supporters of euthanasia may describe this as indirect euthanasia, but again, this term should be discarded when considering the euthanasia debate. [3]

Legal situation of active voluntary euthanasia and assisted suicide

In Australia, active voluntary euthanasia, assisted suicide and physician-assisted suicide are illegal (see Table 1). [1] In general, across all Australian states and territories, any deliberate act resulting in the death of another person is defined as murder. [2] The prohibition of euthanasia and assisted suicide is established in the criminal legislation of each Australian state, as well as the common law in the common law

Table 1. The criminalisation of euthanasia in Australian states and territories.

State or territory	Criminal legislation outlawing euthanasia and assisted suicide
Australian Capital Territory	Crimes Act 1900
New South Wales	Crimes Act 1900
Northern Territory	Criminal Code Act 1983
Queensland	Criminal Code Act 1899
South Australia	Criminal Law Consolidation Act 1935
Tasmania	Criminal Code Act 1924
Victoria	Crimes Act 1958
Western Australia	Criminal Code Act 1913

Table 2. The legalisation of active voluntary euthanasia, assisted suicide and/or physician-assisted suicide in states and countries around the world.

State or country	Legal situation
Netherlands	Active voluntary euthanasia and physician-assisted suicide are permitted under certain conditions pursuant to the <i>Termination of Life on Request and Assisted Suicide (Review Procedures) Act (2002)</i> . [2] The Act creates an exemption from criminal prosecution for physicians who “have complied with the requirements of due care mentioned in the Act” as well as reporting the case. [6] Euthanasia may be performed on adults and in children older than twelve years of age. [1,2]
Belgium	Active voluntary euthanasia is legal under the <i>Act Concerning Euthanasia</i> which came into effect in 2002. Euthanasia can only be granted to those whose suffering involves “a serious and incurable disorder caused by illness or accident.” It imposes an age restriction of eighteen years of age. This Act does not make mention of assisted suicide or physician-assisted suicide. [1, 2]
Switzerland	Euthanasia is illegal, but assisted suicide is not a crime when the motives of the person assisting are for altruistic reasons and not out of self-interest. However, there is no law that regulates this practice. [1]
Luxembourg	Euthanasia is legal under the <i>Palliative Care/Euthanasia Act 2009</i> , where it is regulated by a living will or advanced directive. Doctors need to consult with a colleague to assess whether patients are terminally ill and are suffering from a “grave and incurable condition,” and have repeatedly requested to die. [2]
United States of America • Washington • Oregon • Montana	In Oregon the <i>Death With Dignity Act</i> came into effect in 1997 and in Washington the <i>Washington Death With Dignity Act</i> was passed in 2008. These Acts have remained alive despite challenges in the US Supreme Court. Washington’s and Oregon’s <i>Death With Dignity Acts</i> permit a competent terminally and/or hopelessly ill patient to seek lethal drugs from their doctor. They are required to make two verbal and one written application which need to be accompanied by a witness; and obtain the consent of two doctors. In terms of performing the task, it is the patient who takes the lethal drugs themselves, and the doctor does not administer it. These Acts specifically prohibit euthanasia, which is defined as the administration of lethal drugs to the patient by a person other than the patient. While Montana does not have a law that explicitly permits assisted suicide, a 2009 case in the Montana Supreme Court found that there was nothing within state law that prohibited the practice of assisted suicide. [2]

states of New South Wales, South Australia and Victoria. [2]

The prohibition of euthanasia and assisted suicide in Australia has been the status quo for many years now. However, there was a period when the Northern Territory permitted euthanasia and physician-assisted suicide under the *Rights of Terminally Ill Act (1995)*. The Act came into effect in 1996 and made the Northern Territory the first place in the world to legally permit active voluntary euthanasia and physician-assisted suicide. Under this Act, competent terminally ill adults who were aged 18 or over, were able to request a physician to help them in dying. This Act was short-lived however, after the Federal Government overturned it in 1997 with the *Euthanasia Laws Act 1997*. [1,2] The *Euthanasia Laws Act 1997* denied states the power to legislate to permit euthanasia or assisted suicide. [1] There have been a number of attempts in various Australian states, over the past decade and more recently, to legislate for euthanasia and assisted suicide, but all have failed to date, owing to a majority consensus against euthanasia. [1]

A number of countries and states around the world have permitted euthanasia and/or assisted suicide in some form; however this is often under specific conditions (see Table 2).

Arguments for and against euthanasia

There are many arguments that have been put forward for and against euthanasia. A few of the main arguments for and against euthanasia are outlined below.

For

Rights-based argument

Advocates of euthanasia argue that a patient has the right to make the decision about when and how they should die, based on the principles of autonomy and self-determination. [1, 5] Autonomy is the concept that a patient has the right to make decisions relating to their life so long as it causes no harm to others. [4] They relate the notion of autonomy to the right of an individual to control their own body, and should have the right to make their own decisions concerning how and when they will die. Furthermore, it is argued that as part of our human rights, there is a right to make our own decisions and a right to a dignified death. [1]

Beneficence

It is said that relieving a patient from their pain and suffering by performing euthanasia will do more good than harm. [4] Advocates of euthanasia express the view that the fundamental moral values of society, compassion and mercy, require that no patient be allowed to suffer unbearably, and mercy killing should be permissible. [4]

The difference between active euthanasia and passive euthanasia

Supporters of euthanasia claim that active euthanasia is not morally worse than passive euthanasia - the withdrawal or withholding of medical treatments that result in a patient’s death. In line with this view, it is argued that active euthanasia should be permitted just as passive euthanasia is allowed.

James Rachels [12] is a well-known proponent of euthanasia who advocates this view. He states that there is no moral difference between killing and letting die, as the intention is usually similar based on a utilitarian argument. He illustrates this argument by making use of two hypothetical scenarios. In the first scenario, Smith anticipates an inheritance should anything happen to his six-year-old cousin, and ventures to drown the child while he takes his bath. In a similar scenario, Jones stands to inherit a fortune should anything happen to his six-year-old cousin, and upon intending to drown his cousin, he witnesses his cousin drown on his own by accident and lets him die. Callahan [9] highlights the fact that Rachels uses a hypothetical case where both parties are morally culpable, which fails to support Rachels’ argument.

Another of his arguments is that active euthanasia is more humane than passive euthanasia as it is “a quick and painless” lethal injection whereas the latter can result in “a relatively slow and painful death.” [12]

Opponents of euthanasia argue that there is a clear moral distinction between actively terminating a patient’s life and withdrawing or withholding treatment which ends a patient’s life. Letting a patient die from an incurable disease may be seen as allowing the disease to be the natural cause of death without moral culpability. [5] Life-support treatment merely postpones death and when interventions are withdrawn, the patient’s death is caused by the underlying disease. [5]

Indeed, it is this view that is strongly endorsed by the Australian Medical Association, who are opposed to voluntary active euthanasia

and physician-assisted suicide, but does not consider the withdrawal or withholding of treatment that result in a patient's death as euthanasia or physician-assisted suicide. [1]

Against

The sanctity of life

Central to the argument against euthanasia is society's view of the sanctity of life, and this can have both a secular and a religious basis. [2] The underlying ethos is that human life must be respected and preserved. [1]

The Christian view sees life as a gift from God, who ought not to be offended by the taking of that life. [1] Similarly the Islamic faith says that *"it is the sole prerogative of God to bestow life and to cause death."* [7] The withholding or withdrawal of treatment is permitted when it is futile, as this is seen as allowing the natural course of death. [7]

Euthanasia as murder

Society views an action which has a primary intention of killing another person as inherently wrong, in spite of the patient's consent. [8] Callahan [9] describes the practice of active voluntary euthanasia as *"consenting adult killing."*

Abuse of autonomy and human rights

While autonomy is used by advocates for euthanasia, it also features in the argument against euthanasia. Kant and Mill [3] believe that the principle of autonomy forbids the voluntary ending of the conditions necessary for autonomy, which would occur by ending one's life.

It has also been argued that patients' requests for euthanasia are rarely autonomous, as most terminally ill patients may not be of a sound or rational mind. [10]

Callahan [9] argues that the notion of self-determination requires that the right to lead our own lives is conditioned by the good of the community, and therefore we must consider risk of harm to the common good.

In relation to human rights, some critics of euthanasia argue that the act of euthanasia contravenes the "right to life". The Universal Declaration of Human Rights highlights the importance that, *"Everyone has the right to life."* [3] Right to life advocates dismiss claims there is a right to die, which makes suicide virtually justifiable in any case. [8]

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The role of palliative care

It is often argued that pain and suffering experienced by patients can be relieved by administering appropriate palliative care, making euthanasia a futile measure. [3] According to Norval and Gwynter [4] *"requests for euthanasia are rarely sustained after good palliative care is established."*

The rights of vulnerable patients

If euthanasia were to become an accepted practice, it may give rise to situations that undermine the rights of vulnerable patients. [11] These include coercion of patients receiving costly treatments to accept euthanasia or physician-assisted suicide.

The doctor-patient relationship and the physician's role

Active voluntary euthanasia and physician-assisted suicide undermine the doctor-patient relationship, destroying the trust and confidence built in such a relationship. A doctor's role is to help and save lives, not end them. Casting doctors in the role of administering euthanasia *"would undermine and compromise the objectives of the medical profession."* [1]

Conclusion

It can be seen that euthanasia is indeed a contentious issue, with the heart of the debate lying at active voluntary euthanasia and physician-assisted suicide. Its legal status in Australia is that of a criminal offence, conferring murder or manslaughter charges according to the criminal legislation and/or common law across Australian states. Australia's prohibition and criminalisation of the practice of euthanasia and assisted suicide reflects the legal status quo that is present in most other countries around the world. In contrast, there are only a few countries and states that have legalised acts of euthanasia and/or assisted suicide. The many arguments that have been put forward for and against euthanasia, and the handful that have been outlined provide only a glimpse into the ethical debate and controversy surrounding the topic of euthanasia.

Conflicts of interest

None declared.

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Graded exposure to neurophobia: Stopping it affect another generation of students

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Neurophobia

Neurophobia has probably afflicted you at some stage during your medical school training, whether figuring out how to correlate signs elicited from examination with a likely diagnosis, or deciphering which tract has decussated at a particular level in the neuroaxis. The disease definition of neurophobia as the 'fear of neural sciences and clinical neurology' is a testament to its influence; affecting up to 50% of students and junior doctors at least once in their lifetime. [1] The severity of the condition ranges from simple dislike or avoidance of neurology to sub-par clinical assessment of patients with a neurological complaint. Neurophobia is often compounded by a crippling lack of confidence in approaching and understanding basic neurological concepts.

According to the World Health Organisation, neurological conditions contribute to about 6.3% of the global health burden and account for as much as twelve percent of global mortality. [2] Given these figures, neurophobia persisting into postgraduate medical years may adversely influence the treatment that the significant proportion of patients who present with neurological complaints receive. This article will explore why neurophobia exists and some strategies in remedying it from both a student and teaching perspective.

Perceptions of neurology

One factor contributing to the existence of neurophobia is the perception of neurology within the medical community. The classic stereotype, so vividly depicted by the editor of the British Medical Journal: 'the neurologist is one of the great archetypes: a brilliant, forgetful man with a bulging cranium....who....talks with ease about bits of the brain you'd forgotten existed, adores diagnosis and rare syndromes, and - most importantly - never bothers about treatment.' [3] The description by Talley and O' Connor is that of the neurologist being identified by the presence of hatpins in their expensive suits; and how they use the keys of an expensive motor car to elicit plantar reflexes further solidifies the mythology of the neurologist as a stereotype for another generation of Australian medical students.



[4] Some have even proposed that neurologists thrive in a specialty known for its intellectual pursuits and exclusivity – a specialty where 'only young Einsteins need apply.' [5] Unfortunately, these stereotypes may only serve to perpetuate the reputation of neurology as a difficult specialty, which is complex and full of rare diagnoses (Figure 1).

However, everyone knows that stereotypes are almost always inaccurate. An important question is what do students really think about neurology? There have been several questionnaires asking this question to medical students across various countries and the results are strikingly similar in theme. Neurology is considered by students as the most difficult of the internal medicine specialties. Not surprisingly, it was also the specialty perceived by medical students as the one they had the least knowledge about and, understandably, were least confident in. [5-10] Yet such sentiments are also shared amongst residents, junior doctors and general practitioners in the United Kingdom (UK) and United States (US). [8-10] The persistence of this phenomenon after medical school is supported by the number of intriguing and difficult case reports published in the prestigious Lancet journal. Neurological cases (26%) appear at more than double the frequency of the next highest specialty, gastroenterology, (12%) as a proportion of total case reports in the Lancet from 2003 to 2008. [11] However, this finding may also be explained by the fact that in one survey, neurology was ranked as the most interesting of specialties by medical students, especially after they had completed a rotation within the specialty. [10] So whilst neurophobia exists, it is not outlandish to claim that many medical students do at least find neurology very interesting and would therefore actively seek to improve their understanding and knowledge.

The perception of neurological disease amongst students and the wider community can also be biased. Films such as *The Diving Bell and the Butterfly* (2007), which is about locked-in syndrome, are not only a compelling account of a peculiar neurological disease, capturing the imagination of the public, but they also highlights the absence of effective treatment following established cerebral infarction. Definitive cures for progressive illnesses, including multiple sclerosis and motor neuron disease are also yet to be discovered, but the reality is that there are numerous effective treatments for a variety of neurological complaints and diseases. Some students will thus incorrectly perceive that the joy gained from neurology only comes from the challenge of arriving at a diagnosis rather than from providing useful treatment to patients.

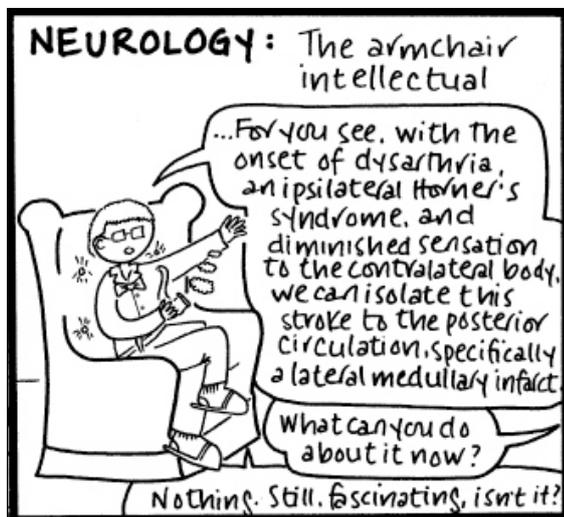


Figure 1. A cartoon depiction of a stereotypical neurologist – adapted from the 12 specialty stereotype cartoon. Printed with permission of Michelle Au MD (www.michelleau.com)

Other causes of neurophobia

Apart from the perception of neurology, a number of other reasons for students' neurophobia and the perceived difficulty of neurology have been identified. [5-10] Contributory factors to neurophobia can be divided into pre-clinical and clinical exposure factors. Pre-clinical factors include inadequate teaching in the pre-clinical years, insufficient knowledge of basic neuroanatomy and neuroscience, as well as difficulty in correlating the biomedical sciences with neurological cases (especially localising lesions). Clinical exposure factors include the length of the neurology examination, a perception of complex diagnoses stemming from inpatients being a biased sample of neurology patients, limited exposure to neurology and a paucity of bedside teaching.

Preventing neurophobia – student and teacher perspective

It is clearly much better to prevent neurophobia from occurring than to attempt to remedy it once it has become ingrained. Addressing pre-clinical exposure factors can prevent its development early during medical school. Media reports have quoted doctors and students bemoaning the lack of anatomy teaching contact hours in Australian medical courses. [12, 13] Common sense dictates that the earlier and more frequent the exposure that students have with basic neurology in their medical programs (for example, in the form of introductory sessions on the brain, spinal cord and cranial nerves that are reinforced later down the track), the greater the chance of preventing neurophobia in their clinical years. It goes without saying that a fundamental understanding of neuroanatomy is essential to localising lesions in neurology. Clinically-relevant neurosciences should likewise receive emphasis in pre-clinical teaching.

Many neurology educators concur with students' wishes for the teaching of basic science and clinical neurology to be effectively integrated. [14, 15] This needs to be a priority. The problem or case based learning model adopted by many undergraduate programs should easily accommodate this integration, using carefully selected cases that can be reinforced with continual assessments via written or observed clinical exams. [15] Neuroanatomy can be a complex science to comprehend. Therefore, more clinically-appropriate and student-focused rules or tricks should be taught to simplify the concepts. The 'rule of fours' for brainstem vascular syndromes is one delightful example of such a rule. [16] This example of a teaching 'rule' would be more useful for students than memorising anatomical mnemonics, which favour rote learning over developing a deeper understanding of anatomical concepts. Given the reliance on more and more sophisticated neuroimaging in clinical neurology, correlating clinical neuroimaging with the relevant anatomical concepts must also be included in the pre-clinical years.

During the clinical years, medical students ideally want more frequent and improved bedside teaching in smaller tutorial groups. The feasibility of smaller groups is beyond the scope of my article but I will emphasise one style of bedside teaching that is most conducive to learning neurology. Bedside teaching allows the student to carry out important components of a clinical task under supervision, test their understanding during a clinical discussion and then reflect on possible areas of improvement during a debrief afterwards. This century-old style of bedside teaching, which has more recently been characterised in educational theory as the application of an experiential learning cycle (ELC) framework, works for students and as it did for their teachers when they themselves were students of neurology. [17, 18] The essential questions for a clinical teacher to ask during bedside tutorials are 'why?' and 'so what?' These inquiries will gauge students' deeper understanding of the interactions between an illness and its neuro-anatomical correlations, rather than simply testing recall of isolated medical facts. [19]

There is also the issue of the inpatient population within the neurology ward. The overwhelming majority of patients are people who have experienced a stroke and, in large tertiary teaching hospitals, there

will also be several patients with rare diagnoses and syndromes. This selection of patients is unrepresentative of the broad nature of neurological presentations and especially excludes patients whose conditions are non-acute and who are referred to outpatients' clinics. Students are sometimes deterred by patients with rare syndromes that would not even be worth mentioning during a differential diagnosis list in an objective structured clinical examination. Therefore, more exposure to outpatient clinics would assist students to develop skills in recognising common neurological presentations. The learning and teaching of neurology at outpatients should, like bedside tutorials, follow the ELC model. [18] Outpatient clinics should be made mandatory within neurology rotations and rather than making students passive observers, as is commonplace, students should be required to see the patient beforehand (especially if the patient is a patient known to the neurologist with signs or important learning points that can be garnered in their history). A separate clinic room for the student is necessary for this approach, with the neurologist then coming in after a period of time, allowing the student to present their findings followed by an interactive discussion of relevant concepts. Next, the consultant can conduct the consultation with the student observing. Following feedback, the student can think about what can be improved and plan the next consultation, as described in the ELC model (Figure 2). Time constraints make teaching difficult in outpatient settings. However, with this approach, when the student is seeing the known patient by themselves, the consultant can see other (less interesting) patients in the clinic so in essence no time (apart from the teaching time) is lost. This inevitably means the student may miss seeing every second patient that comes to the clinic but in this case, sacrificing quantity for quality of learning may be more beneficial in combating neurophobia long term.

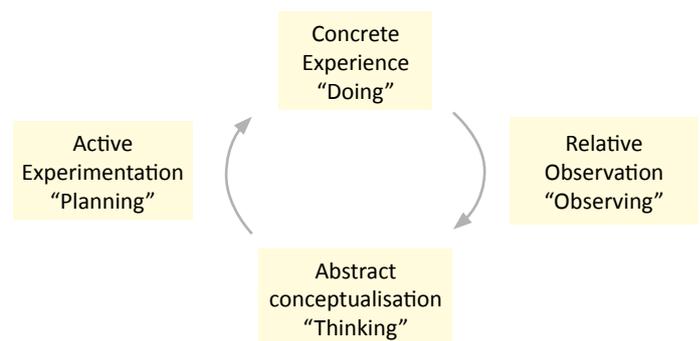


Figure 2. Experiential learning cycle [18] – how students should learn from bedside and clinical encounters.

Neurology associations have developed curricula in the US and UK as a "must-know" guideline for students and residents. [20, 21] The major benefits of these endeavours are to set a minimum standard across medical schools and provide clear objectives to which students can aspire. This helps develop recognition of common neurological presentations and the acquisition of essential clinical skills. It is for this reason that the development of a uniform neurology curriculum adopted through all medical school programs across Australia may also alleviate neurophobia.

The responsibility to engage or seek learning opportunities in neurology, to combat neurophobia, nevertheless lies with the students. Students' own motivation is vital in seeking improvement. It is often hardest to motivate students who find neurology boring and thus fail to engage with the subject. Nevertheless, interest often picks up once students feel more competent in the area. To help improve knowledge and skills in neurology, students can now use a variety of resources apart from textbooks and journals to complement their clinical neurology exposure. One growing trend in the US is the use of online learning and resources for neurology. A variety of online resources supplementing bedside learning and didactic teaching (e.g. lectures) is beneficial to

students because of the active learning process they promote. This involves integrating the acquisition of information, placing it in context and then using it practically in patient encounters. [9] Therefore, medical schools should experiment with novel resources and teaching techniques that students will find useful – ‘virtual neurological patients’, video tutorials and neuroanatomy teaching computer programmes are all potential modern teaching tools. This new format of electronic teaching is one way to engage students who otherwise are uninterested in neurology. In conclusion, recognising the early signs of neurophobia is important for medical students and teachers alike. Once it is diagnosed, it is the responsibility of both student and

teacher to minimise the burden of disease.

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Immunology beyond a textbook: Psychoneuroimmunology and its clinical relevance for psychological stress and depression

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In his fourth year of medicine at the University of Tasmania, Adrian is currently an Honours research candidate. His general and research interests encompass molecular and cellular immunobiology, clinical immunology, medical education and infection control. The primary aim of writing this article was to show how basic immunology can form the basis of many clinical encounters.

Our medical studies encompass many areas of medical science, and immunology is an example of just one. Traditionally, we have been taught that our immune system exists to protect us from pathogens; however, in recent years, this romantic view of the immune system has been challenged and it is now well recognised that it is also involved in whole-body homeostasis and cross talks to other regulating systems of the body. This is the notion of psychoneuroimmunology (PNI). This text will briefly review the current understanding of PNI and how it features prominently in clinical practice as a part of the 'whole person' model of patient care and, especially, in terms of stress and depression. With this in mind, PNI is an emerging medical discipline that warrants integration and consideration in future medical care and practice.

Introduction

At first glance, immunology may be viewed by some as an esoteric medical science that simply provides us with the molecular and cellular mechanisms of disease and immunity. It is a subject that all medical students have to face and no doubt can find quite challenging as well. Yet, in recent times, its role in helping us understand mental health and why individuals behave in certain ways has become increasingly appreciated. [1,2] The novel area of study that attempts to explain this intricate and convoluted relationship between the mind, behaviour, nervous system, endocrine system and finally the immune system is, quite appropriately, termed psychoneuroimmunology (PNI) or sometimes psychoendoneuroimmunology. [3] This was probably something that was never mentioned during our studies because it is quite radical and somewhat ambiguous. So what, then, is PNI all about and why is it important?

Many of us may have come across patients that epitomise the association between mental disturbances and physical manifestations of disease. Indeed, it is this biopsychosocial model that is well documented and instilled into the minds of medical students. [4-7] The mechanism behind this, although something best left to science, is nonetheless interesting to know and appreciate as medical students. This is PNI.

The basic science of psychoneuroimmunology

History

The notion that behaviour and the manifestation of disease were linked was probably first raised by Galen (129-199 AD) who noticed that melancholic women were more likely to develop breast cancer than sanguine women. [8] The modern push for PNI probably began in the 1920s to 1930s when Metal'nikov and colleagues conducted several preliminary experiments in various animals showing that the immune system can be classically conditioned. [9] New interest in this area was established by Solomon *et al.* who, in 1964, coined the term 'psychoimmunology' [10]; however, the concept of PNI was firmly established by the American behavioural scientist Dr Robert Ader in his revolutionary 1981 book, 'Psychoneuroimmunology.' This book described the dynamic molecular and clinical manifestations of PNI through various early experiments. [11,12] In one initial experiment, Ader and fellow researchers successfully demonstrated that the immune system can be conditioned, similarly to Metal'nikov. After pairing saccharin with the immunosuppressive agent,



cyclophosphamide, and administering this to some rats, they found that saccharin administration alone, at a later date, was able to induce an immunosuppressive state marked by reduced titres of haemagglutinating antibodies to injected sheep erythrocytes. [13] The authors postulated that non-specific stress associated with the conditioning process would have elicited such a result. By extension and based on earlier research, [14] the authors believed psychological, emotional or physical stress probably act through hypothalamic pathways to induce immunomodulation which manifests itself in various ways. [13]

Stress, depression and PNI

A prominent aspect of PNI focuses on the bi-directional relationship between the immune system and stress and depression, where one affects the other. [4,15] The precise mechanisms are complicated but are ultimately characterised by the stress-induced dysregulation, (either activation or depression), of the hypothalamic-pituitary-adrenal (HPA) and sympathetic-adrenal-medullary (SAM) axes. [16] Because of the pleiotropic effects of these hormones, they can induce a dysfunctioning immune system partly through modulating the concentration of certain cytokines in the blood. [15] Endocrine and autonomic pathways upregulate pro-inflammatory cytokines (such as interleukin (IL)-1 β , IL-6 and tumour necrosis factor- α (TNF- α)) that can exert their effects at the brain through direct (i.e., circumventricular organs) and indirect access ports (via afferent nerve fibres). [17,18] Such pro-inflammatory cytokines therefore stimulate the HPA axis and activate it leading to the rapid production of corticotropin-releasing hormone. [19-21] Eventually, cortisol is produced which, in turn, suppresses the pro-inflammatory cytokines. Interestingly, receptors for these cytokines have also been found on the pituitary and adrenal glands, thereby serving the ability to integrate neuroendocrine signals at all three levels of the HPA axis. [21,22] Cortisol also has significant effects on mood, behaviour and cognition. On a short-term basis, it may be beneficial; making an animal more alert and responsive. However, increased periods of elevation may give rise to impaired cognition, fatigue and apathy. [23]

In the brain, an active role is played by the once-thought insignificant glial cells which participate at the so-called tripartite synapse (glial cell plus pre- and post-synaptic neurons). [24] It is this unit that is fundamental to much of the central nervous system activity of the PNI system. Pro-inflammatory cytokines like interferon (IFN)- α and IL-1 β released from peripheral and central (microglia and astrocytes) sources can alter dopaminergic signals, basal ganglial circuitry, hippocampal

functioning and so on. Consequently, this induces behavioural changes of anhedonia, memory impairment and other similar behaviours. [18,25] Since IFN- α receptors have been found on microglia in the brain, [26] IFN- α likely also causes further local inflammation and further disruption of dopaminergic signals. Excessively activated microglia by a range of inflammatory cytokines can therefore cause direct neurotoxicity and neuropathology. [27] Additionally, these cytokines can induce activity of the indoleamine 2,3-dioxygenase enzyme (found in astrocytes and microglia) which metabolise the precursor of serotonin, tryptophan. The result is a reduction of serotonin and the production of various products, including quinolinic acid, an NMDA (N-methyl-D-aspartate) receptor agonist which leads to excess glutamate and neurodegeneration. These mechanisms are postulated to contribute to the pathogenesis of depression; however, the precise mechanisms of which are yet to be fully elucidated. [28-30]

Recent research into behavioural epigenetics has also provided an additional interesting link whereby stressors to the psychosocial environment can modulate gene expression within the neuroimmune, physiological and behavioural internal environments. This may account for the long-term aforementioned changes in immune function. [31]

Depression has also been shown to activate the HPA and SAM axes as well through inflammatory processes, [28,32] which in turn exacerbates any pre-existing depressive behaviours. [33] This inflammatory theory of depression sheds light onto the complicated pathophysiology of depression, adding to the already well-characterised theory of serotonergic neurotransmission deficiency. [28,33] Interestingly, pro-inflammatory cytokines have been shown to modulate serotonergic activity in the brain as well, [34,35] which provides further insight into this complex disorder. There is question as to whether or not this may have its roots with evolution where the body diverts energy resources away from other areas to the immune system for the promotion of anti-pathogenic activity during stress and depression. [17] For instance, with threat of an injury or wound in an acute situation (the stressor), cortisol (a natural immunosuppressant) would be released via the HPA axis. This aids in energy conservation which in turn, and paradoxically, attempts to minimise the non-helpful effect of immunosuppression in times of infection risks. [17] Depressive behaviour such as lethargy has also been said to have stemmed from the need to conserve energy to promote fever and inflammation. [2] Ultimately, the evolutionary aspects of PNI are under current speculation and investigation to elicit the precise links and relationships. [36]

The alterations of the immune system in stress and depression have implications for other areas of medicine as well. Though conclusive clinical experiments are lacking, it has been strongly hypothesised that this imbalanced immune state can contribute to a plethora of medical ailments. Depression, characterised by a general pro-inflammatory state with oxidative and nitrosative stress, [33,37] can contribute to poor wound healing; and exacerbate chronic infections and pain. [38,39] Stress similarly entails a dysregulated immune system and may contribute to the aforementioned conditions plus cardiovascular disease and minor infectious diseases such as the common cold. [40-44] The link with cancer is somewhat more controversial but both may, in some way, predispose to the development of it through numerous mechanisms such as reduced immune surveillance by immune cells (cytotoxic T cells and natural killer cells), general inflammation and genomic instability. [45,46]

Highlighting the bidirectionality of the PNI paradigm, secondary inflammation caused by a myriad of neurological diseases (e.g., Huntington's disease, Alzheimer's disease) and local and systemic disorders (e.g., systemic lupus erythematosus, stroke, cardiovascular disease and diabetes mellitus) may very well contribute to the pathogenesis of co-existing depression. [47] This may account for the close association of depression and such diseases. Underlying neurochemical changes have been observed in many of these diseases—especially the neurological disease examples—and it has been suggested that depression vulnerability is proportional to how

well one can 'adapt' to said neurochemical imbalances. [48,49]

Through an immunophysiological point-of-view, these links certainly makes sense; but it is important to note that there could be other confounding factors, such as increased alcohol consumption and other associated behaviours that accompany stress and depression that can contribute to pathology. [50] The question therefore remains as to how much the mind plays in the pathogenesis of physical ailments.

Figure 1 summarises the general PNI model as it relates to stress and depression.

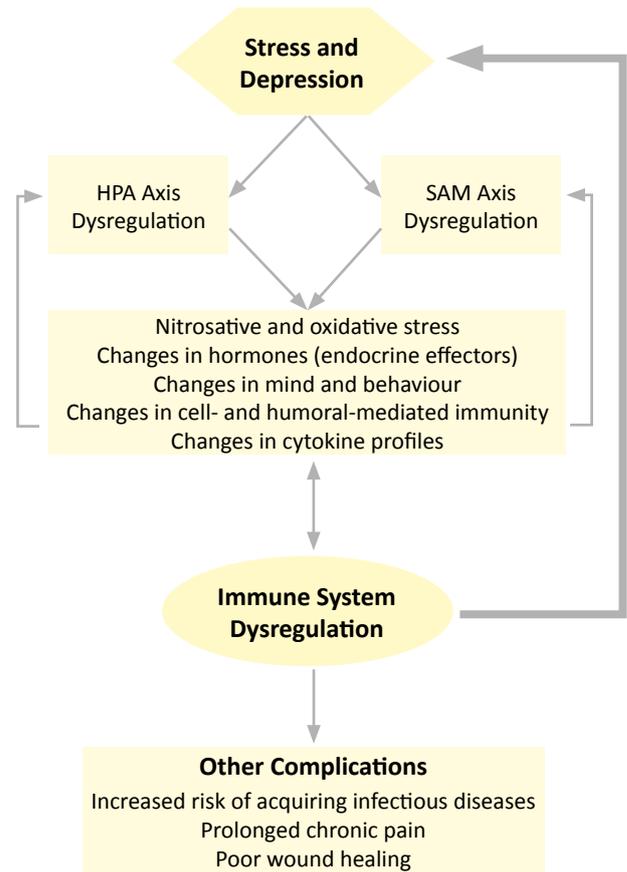


Figure 1. A summary of the processes involved in stress-induced dysregulation of the immune system and consequences. Note the bi-directional relationship between the immune system and stress/depression. HPA – hypothalamic-pituitary-adrenal; SAM – sympathetic-adrenal-medullary.

Implications

Having explored the discipline of PNI, what is the importance of this for clinical practice? Because of the links between stress and depression; altered immunity; other ill-effects and behaviour, [3,12] it seems fitting that if we can address a patient's underlying stress or depression, we may be able to improve the course of their illness or prevent, to a certain extent, the onset of certain diseases by correcting immune system dysregulation. [43]

Simply acknowledging the relationship between stress and their role in the pathogenesis, maintenance and susceptibility of diseases is certainly not enough, and healthcare professionals should consider the mental state of mind for every patient that presents before them. It is fortunate, then, that a myriad of simple stress-management strategies could be employed to improve their mental welfare, depending on their individual circumstances. Such strategies include various relaxation techniques, meditation, tai chi, hypnosis and mindfulness practice. These have, importantly, proven cost-effective and lead to self-care and self-efficacy. [51,52]

As an example, mindfulness has received considerable attention in its role of alleviating stress and depression. [52] Defined as the increased awareness and attention to present, moment-to-moment

thoughts and experiences, mindfulness therapy has shown remarkable efficacy in the promotion of positive mental states and quality of life. [52-54] This is particularly important in this age of chronic diseases and their associated unwelcomed psychological consequences. [54] Furthermore, and in light of the discussion above on PNI, there is evidence that mindfulness practice induces physiological responses in brain and immune function. [55,56] This suggests that its benefits are mediated, at least in part, through such positive immunological alterations that modulate disease processes.

With the growing understanding of the cellular and molecular mechanisms behind stress, depression and other similar psychiatric disorders, a host of novel pharmacological interventions to target the previously discussed biological pathways are actively being researched. Most notably is the proposition of the role of anti-inflammatories in ameliorating such conditions where patients present in an increased inflammatory state. This is largely based on experimental work where antagonists to pro-inflammatory cytokines and/or their receptors improve sickness behaviours in animals. [17] As an example, the cholesterol-lowering statins have been found to have intrinsic anti-inflammatory and antioxidant properties. In a study of patients taking statins for cardiovascular disease, it was found that statins had a substantial protective effect on the risk of developing depression. This suggests that the drug acts, at least in part, to decrease systemic inflammatory and oxidative processes that characterise depression. [57] Other drugs being researched aim to tackle additional pathways such as those involving neurotransmitters and their receptors.

Of the neuroendocrine arm of PNI, current research is looking at ways to reverse HPA axis activation. [20] Some tested drugs that act on specific parts of the HPA axis seem to show promise; however, a major problem is tailoring the correct drug to the correct patient, for not all patients will present with the same neuroendocrine profile. [58,59] Neuroendocrine manipulation can also be used to treat or act as an adjunct to other non-HPA axis-mediated diseases. For example, administration of melatonin and IL-2 was able to increase the survival time in patients with certain solid tumours. [60] Needless to say, a great amount of research is further warranted to test and understand possible pharmaceutical agents.

Discussion and Conclusion

The exciting and revolutionary field of PNI has now provided us with the internal links of all the major regulating systems of the human body. The complex interactions that take place is, indeed, a tribute to the complexity of our design, and has provided a basis or mechanism of how our mind and behaviour can influence our physical health. As a result, serious stressors—be them emotional, mental or physical—can wreak havoc on our delicate internal environment and predispose to

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physical ailments, which can further exacerbate the inciting stressors and our mental state. For said psychological stress or depression, it seems appropriate that if healthcare professionals can ameliorate the severity of these, they may be able to further improve the physical health of an individual. How much so is a matter of debate and further investigation. Conversely, as demonstrated by the bi-directionality model of PNI, addressing or 'fixing' the organic pathology may be conducive to the mental state of patients' minds.

Whilst clinical approaches have been sharply juxtaposed to a very theoretical and scientific review of PNI, this has been deliberately done to hopefully demonstrate how mind-body therapies can exert their physical benefits. Accordingly, valued mind-body therapies deserve as much attention as the scientific study of molecular pharmacology. It is also important to note that even these two approaches (pharmacology and mind-body therapies) are almost certainly the tip of the iceberg; for there is certainly a vast amount more to be further explored in our therapeutic approach to medical conditions. For example, how does a practitioner-patient relationship fit into this grand scheme of things, and how much of a role does it play? No doubt a decent part for sure. Furthermore, whilst the PNI framework provides good foundations for which to explain, (at a basic level), the mechanisms behind the development of stress, depression and associated ailments, further insight is needed into the biological basis of these. For example, a symphony of intricate factors (such as the up-regulation of inflammation-induced enzymes, neurotransmitter changes, dysfunction of intracellular signalling, induced autoimmune activity, neurodegeneration and decreased serum levels of antioxidants and zinc) are at play for the signs and symptoms of depression. [61,62] Thus, the complex pathogenesis of psychological stress and depression begs for further clinical and scientific research into unravelling its mysteries. Nevertheless, with a sound basis behind mindfulness, other similar mind-body therapies and novel pharmacological approaches, it seems suitable for these to be further integrated into primary care [54] and other areas of medicine as an adjuvant to current treatments. If we can achieve this, then medicine undoubtedly has more potent tools in its armamentarium of strategies to address and alleviate the growing burden of chronic disease.

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Conflicts of interest

None declared.

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Is there a role for end-of-life care pathways for patients in the home setting who are supported with community palliative care services?

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The concept of a “good death” has developed immensely over the past few decades and we now recognise the important role of palliative care services in healthcare for the dying, our most vulnerable population. [1-3] In palliative care, end-of-life care pathways have been developed to transfer the gold standard hospice model of care for the dying to other settings, addressing the physical, psychosocial and practical issues surrounding death. [1,4] Currently, these frameworks are used in hospitals and residential aged-care facilities across Australia. [1] However, there is great potential for these pathways to be introduced into the home setting with support from community palliative care services. This could help facilitate a good death for these patients in the comfort of their own home, and also support their families through the grieving process.

Although there is no one definition of a “good death”, many studies have examined factors considered important at the end-of-life by patients and their families. Current literature acknowledges that terminally ill patients highly value adequate pain and symptom management, avoidance of prolongation of death, preparation for end-of-life, relieving the burden imposed on their loved ones, spirituality, and strengthening relationships with health professionals through acknowledgement of imminent death. [2] Interestingly, the Steinhäuser study noted a substantial disparity in views on spirituality between physicians and patients. [3] Physicians were found to rank good symptom control as most important, whilst patients considered spiritual issues to hold equal significance. These studies highlight the individual nature of end-of-life care, which reflects why the holistic approach of palliative care can improve the quality of care provided.

It is recognised that patients with life-limiting illnesses have complex needs that often require a multidisciplinary approach with multiple care providers. [1] However, an increased number of team members also creates its own challenges, and despite the best intentions, care can often become fragmented due to poor interdisciplinary communication. [5] This can lead to substandard end-of-life care with patients suffering prolonged and painful deaths, and receiving unwanted, expensive and invasive care, as demonstrated by the Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments (SUPPORT). [6] Temel *et al.* also demonstrated that palliative care can improve the documentation of advanced care directives. [7] For terminally ill patients, this is essential in clarifying and enabling patients’ wishes regarding end-of-life to be respected.

In 2010, Temel *et al.* conducted a randomised controlled trial in patients with newly diagnosed metastatic non-small-cell lung cancer, comparing the effect of palliative care and standard oncologic therapy, to standard oncologic therapy alone. [7] Results demonstrated that palliative care intervention improves quality of life and reduces rates of depression, consistent with existing literature. [7] Furthermore, despite receiving less aggressive end-of-life care, the additional early involvement of palliative care services resulted in a significant prolongation of life, averaging 2.7 months ($p = 0.02$). [7] This 30% improved survival benefit is equivalent to that achieved with a response to standard chemotherapy regimens, which has profound significance for patients with metastatic disease. [7] This study thereby validates the benefits of early palliative care intervention in oncology patients. In addition, early palliative intervention encourages advance care planning, allowing treating teams to elicit and acknowledge patient preferences regarding end-of-life care.



Many physicians often find it difficult to discuss poor prognoses with patients, potentially leaving patients and their families unaware of their terminal condition, despite death being anticipated by the treating team. [1,4] Many health care professionals are uncomfortable discussing death and dying, citing lack of training and fear of upsetting the patient. [8] Regardless, patients are entitled to be informed and supported through this difficult time. In addition, terminal patients and their caregivers are often neglected in decisions about their care, [9] despite their fundamental legal and ethical right to be involved, and studies indicate that they often want to be included in such discussions. [1,10,11] With the multitude of patient values and preferences for care, it can often be difficult to standardise the care provided. End-of-life care pathways encourage discussion of prognosis, facilitating communication that allows patients’ needs to be identified and addressed systematically and collaboratively. [1]

End-of-life care pathways provide a systematic approach and a standardised level of care for patients in the terminal phase of their illness. [1] This framework includes documentation of discussion with the patient and carers of the multi-disciplinary consensus that death is now imminent and life-prolonging treatment is futile, and also provides management strategies to address the individual needs of the dying. There is limited evidence to support the use of end-of-life care pathways, however we cannot discount the substantial anecdotal benefits. [1,12] The lack of high-quality studies indicates a need for further research. [1,12] When used in conjunction with clinical judgment, these pathways can lead to benefits such as: improved symptom control, earlier acknowledgement of terminal prognosis by the patient and family, prescription of medications for end-of-life, and aiding the grieving process for relatives. [1,12,13] As such, end-of-life care pathways are highly regarded in palliative care, transferring the benchmarked hospice model of care of the dying into other settings, [14] and have been widely implemented nationally and internationally. [1]

The most recognised and commonly used end-of-life care pathway is the Liverpool Care Pathway (LCP), which was developed in the United Kingdom to transfer the hospice model of care for the dying to other care settings. [13,15] It has been implemented into hospices, hospitals and aged care facilities, and addresses the physical, psychosocial and spiritual needs of these patients. [1,13,15] In 2008, Verbeek *et al.* examined the effect of the LCP pre- and post-implementation on patients from hospital, aged care and home settings. [13] Results demonstrated improved documentation and reduced symptom

burden as assessed by nurses and relatives, in comparison with the baseline period. [13] Although increased documentation does not necessarily equate to better care, high-quality medical records are essential to facilitate communication between team members and ensure quality care is provided. In this study, staff also reported that they felt the LCP provided a structure to patient care, assisted the anticipation of problems, and promoted proactive management of patient comfort. [13] The LCP has significantly increased the awareness of good terminal care, and has provided a model for the end-of-life care pathways currently in use in hospitals and institutions throughout Australia. [1,4]

Community palliative care services support terminally ill patients at home in order to retain a high quality of life. Recognising the holistic principles of palliative care, these multidisciplinary teams provide medical and nursing care, counselling, spiritual support and welfare supports. In the Brumley trial, which evaluated an in-home palliative care intervention with a multidisciplinary team for homebound terminally ill patients, results demonstrated that the intervention group had greater satisfaction with care, were less likely to visit the emergency department, and were more likely to die in the comforts of their own home. [16] These results infer that the community palliative care team provided a high standard of care where symptoms were well-managed and did not require more aggressive intervention. This prevented unnecessary emergency presentations, potential distress for the patient and family, and allowed better use of resources. This study demonstrates that community palliative care services can significantly improve the quality of care for patients living at home with life-limiting illnesses, however, there is still scope for improvement in the current healthcare system.

End-of-life care pathways are regarded as best practice in guiding care for patients where death is imminent. [1] In Australia, there are a number of these frameworks that have been implemented in hospitals and aged-care facilities, demonstrating an improvement in the quality of care in these settings. However, there are also many terminally ill patients who choose to reside in the comfort of their own home, and are supported by community palliative care services. End-of-life care pathways support a high standard of care, which should be available to all patients, irrespective of where they choose to die. As such, there may be a role for end-of-life care pathways in the home setting, supported by community palliative care services. Introducing already implemented local end-of-life care pathway into the community has great potential to reap similar benefits. Initially, these frameworks would be implemented by the community palliative care team, however, caregivers could be educated and empowered to participate in the ongoing care. This could be a useful means to facilitate communication between treating team members and family, and also empower the patient and family to become more involved in their care.

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The potential benefits of implementing end-of-life care pathways into community palliative care services include those currently demonstrated in the hospital and aged-care settings, however there are potentially further positive effects. By introducing these frameworks into the homes of terminally ill patients, caregivers can also be encouraged to take a more active role in the care of their loved ones. This indirect education for the patient and family can provide a sense of empowerment, and assist them to make informed decisions. Additional potential benefits of these pathways could include a reduction in the number of hospital admissions and emergency department presentations, which would reduce the pressures on our already overburdened acute care services. Empowered family and carers could also assist with monitoring, providing regular updates to the community palliative care team, which could potentially lead to earlier detection for when more specialised care is required. The documentation within the pathways could also allow for a smoother transition to hospices if required, and prevent unnecessary prolongation of death. This may translate to prevention of significant emotional distress for the patient and family in an already difficult time, and promote more effective use of limited hospital resources. Integrating end-of-life care pathways into community palliative care services has many potential benefits for patients at home with terminal illnesses, and should be considered as an option to improve the delivery of care.

Palliative care can significantly improve the quality of care provided to patients in the terminal phase, which can be guided by end-of-life care pathways. Evidence validates that these pathways encourage a multidisciplinary change in practice that facilitates a "good death", and supports the family through the bereavement period. In the community, this framework has the potential to empower patients and their caregivers, and assist them to make informed decisions regarding their end-of-life care, thereby preventing unwanted aggressive intervention and unnecessary prolongation of death. However, there is a need for further high-quality studies to validate the anecdotal benefits of these pathways, with potential for a randomised controlled trial investigating the use of end-of-life care pathways in the home setting in Australia. In conclusion, the introduction of end-of-life care pathways into community palliative care services has great potential, particularly if supported and used in conjunction with specialist palliative care teams.

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Conflicts of interest

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The only medical science textbook you need to buy?

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Toby has a background in molecular biology and has worked on cancer epigenetics and microRNAs. His current interests are rural health and emergency medicine. Toby is the treasurer of Sydney University Medical Society and loves the sporting, social and academic medical life at Sydney.

Wilkins R, Cross S, Megson I, Meredith D. *Oxford Handbook of Medical Sciences, Second Edition*. Oxford: Oxford University Press; 2011.

RRP: \$47.95

A complete guide to the medical sciences that fits in your pocket? Including anatomy? It sounds like something you'd find on the bookshop shelf between *Reflexology at Your Fingertips* and *Sex Explained*. But *The Oxford Handbook of Medical Sciences (OHMS)* is probably one of the few serious books that handles this enormous topic and can still be picked up with one hand. The first edition was published in 2006, and it's been a fairly constant companion since I started graduate medicine at Sydney University. The dense but well written text often feels more conducive to medical school than authoritative textbooks - if you're asked to explain a concept in a tutorial, the 30 second answer is better than the five minute dissertation. Compiling principles and systems also means you can flip from say anatomy to immunology without piling up your desk with resources. Unfortunately, the more I've used the first edition the more niggling errors I've come across. Granted most are just typos, but others were more frustrating. Including a colour DNA sequencing output that seems more CSI-prop than medical text, at least to someone with a molecular biology background. And errors like labelling the muscles of mastication as supplied by cranial nerve VIII are inexcusable (instead of V₃ mandibular - so presumably type-setting error). So *OHMS1e* - a great book in serious need of a revision, but could the second edition be the last medical science book you ever buy?

The *OHMS* second edition was published September 2011 from \$35 in online bookshops. On first impression it has not transformed into a full colour extravaganza like the latest Oxford Handbooks of Clinical Medicine/Specialties. It is 40 pages longer than the original, 962 in total, and still small enough for a big pocket. Much of the first edition worked well and it is good to see that the layout remains the same, with each topic generally covered in two pages or less, with plenty of room for annotation. The first three chapters cover the essentials: cells, molecules and biochemistry - with some good looking new

figures. The ten systems-based chapters are now followed by a chapter on medicine and society. The final chapter - techniques of medical sciences - has had a timely rewrite, it won't make you a lab scientist but at least you'll be able to have an intelligent conversation with someone who is. The best addition, in my opinion, are the blue boxes succinctly summarising relevant treatments and drug therapies in all the sections.



The cross-referencing to the most recent clinical Oxford Handbooks is a welcome update (in spite of a couple that refer to OHCM8p.000). I would have liked to see a more thorough reworking of the anatomy section; the diagram of the muscles of the hand remains duplicated a few pages apart. The molecular biology chapter, the one I feel semi-qualified to comment on, is my major complaint. There is no mention of new sequencing technologies and of non-coding RNAs that we are frequently told are the future of the field. Instead Maxam-Gilbert sequencing, a technique probably last done in the 1980s is still covered. Furthermore, 'junk DNA', a term surely killed off by the ENCODE project, makes a vampire-like appearance here. [1]

In summary, if you've already built a reasonable understanding of the medical sciences and are looking for a one-stop book for reference or revision on the run then this book is a good option. For its convenience and conciseness it is hard to beat *OHMS2e*. The USMLE crammers like *First Aid*, offer analogous coverage at an equivalent price but carrying one in your pocket isn't an option. But beware - as far as *OHCM2e* is concerned the muscles of mastication are still innervated by CNVIII. Now where is my anatomy book?

References

[1] Myers RM, Stamatoyannopoulos J, Snyder M, Dunham I, Hardison RC, Bernstein BE, et al. A user's guide to the encyclopedia of DNA elements (ENCODE). *PLoS Biol* 2011 Apr;9(4):e1001046.

Harrison's: Friend or Foe?

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Longo DL, Harrison TR. *Harrison's Principles of Internal Medicine, Eighteenth Edition*. London: McGraw-Hill; 2012.

RRP: \$199

So a review of this text has been done before, not of *Harrison's Principles of Internal Medicine* (Harrison's) in isolation but a comparison to William Osler's *The Principles and Practice of Medicine*. [1] The latest edition of Harrison's has been available since July 2011, and as an avid user of the online version of Harrison's (via AccessMedicine™ through the University's library website). The book is found in two tomes, a whopping 4012 pages in total. I have a thing for being able to physically hold a book and read it, hence not relying on the online edition, which has been previously compared to the text version, as my internet connection is very erratic and the University has a concurrent users policy. [2]

Alas it was a decision that I do regret (to some extent) as I have since found myself referring to Harrison's to find an answer to a problem, whether it be electronically via the DVD given with the book or via flicking through the book itself, and neglecting some other general medicine or specialised texts that I own. This speaks volumes about Harrison's comprehensive nature, but also about my enjoyment of the text.

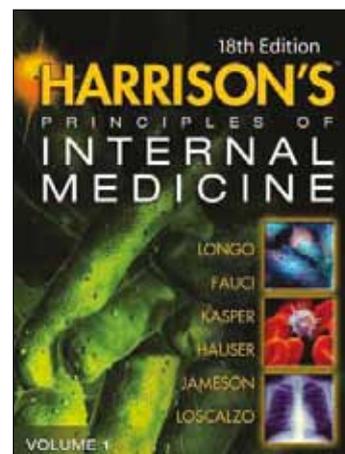
So what do I like about the book? It is detailed, this may speak more about myself than the text but I think that many medical students appreciate this level of detail, if only for interest rather than what is actually required. I mean, do you know of any other books with 395 chapters and another 51 chapters available electronically? I love the detailed explanations of concepts such as "Insulin biosynthesis, secretion and action", which would normally be found in a more specialised text such as Lehninger's *Principles of Biochemistry*™, and pathophysiology of common diseases such as asthma, COPD and myocardial infarction. [3]

The "yellow sections" in the chapters are a great reference for medical students and physicians alike, these are the sections on treatment of certain conditions. The diagrams are great, as are flowcharts, which explain key concepts such as development of a certain condition (for example, ischaemic stroke) or treatment or diagnostic algorithms, such as tuberculosis or HIV/AIDS. The layout of the parts, sections and chapters of the text are very logical and (if you were keen enough) could be read in order for example:

References

- [1] Hogan DB. Did Osler suffer from "paranoia antitherapeuticum baltimorensis"? A comparative content analysis of *The Principles and Practice of Medicine* and *Harrison's Principles of Internal Medicine*, 11th edition. *CMAJ*. 1999 Oct;161(7):842-5.
 [2] DeZee KJ, Durning S, Denton GD. Effect of electronic versus print format and different reading resources on knowledge acquisition in the third-year medicine clerkship. *Teach Learn Med*. 2005;17(4):349-54.
 [3] Powers AC. "Insulin Biosynthesis, Secretion and Action" from *Harrison's Principles of Internal Medicine*. 18 ed. Longo DF, A; Kasper, D; Hauser, S; Jameson, J L; Loscalzo, J, editor. Columbus: McGraw-Hill Medical; 2011.

"Part 10: Disorders of the cardiovascular system, Section 1: Introduction to cardiovascular disorders, Chapter 224: Basic Biology of the Cardiovascular system, Chapter 225: Epidemiology of Cardiovascular disease ... Section 2: Diagnosis of Cardiovascular disorders, Chapter 227: Physical examination of the cardiovascular system, Chapter 228: Electrocardiography ... Section 3: Disorders of rhythm ... Section 4: Disorders of the heart ... Section 5: Vascular disease"



It is easy to see how logically the book is organised, starting from the basics of the given system or group of conditions then working through epidemiology, diagnosis and then finally about the conditions themselves; and given that Part 10 of the book as a whole spans pages 1797 – 2082 (yes, 285 pages) you can gather an appreciation for the detail of the text. Another great feature is the "further readings" given at the end of each chapter citing original and review publications from peer reviewed journals so (if interested) you can read some more about the topic you are interested in.

What don't I like about the book? Having two volumes can sometimes be a little tedious when you pick up one and then find that the topic you want is in the other (although you have to remember page numbers this way, it is still preferable to having one enormous tome with a tiny typeface). The organisation of the text is a double-edged sword as it can get frustrating as when searching for a condition such as polycystic ovarian syndrome (PCOS) this will bring up entries in sections such as: menstrual disorders, biology of obesity, amenorrhoea, metabolic syndrome, hirsutism and virilisation and diabetes mellitus; yet there is no definitive section on PCOS itself as there is for a condition such as pheochromocytoma. Sometimes you open a page, and the amount of text overwhelms you and there are no figures to break it up, which can be quite intimidating for a medical student to find one specific passage or sentence. This isn't too large a problem in my opinion, but I have known students to be put off by books of such a nature.

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