Global View and Sepsis Challenges

Dr Marc Ziegenfuss
29 September 2017
Mindless application of current Knowledge, Beliefs, Opinion, Mood, Habits

New Awareness ➔ Mindful
**Sepsis** is one of the most common, least-recognized illnesses in both the developed and developing world. Globally, 20 to 30 million patients are estimated to be afflicted every year, with over 6 million cases of neonatal and early childhood sepsis and over 100,000 cases of maternal sepsis. Worldwide, a person dies from sepsis every 3-4 seconds.

**Sepsis is a medical emergency !!!!**

The diagnosis and treatment of Sepsis poses a medical emergency. The disease kills more people than AIDS, prostate and breast cancer combined globally.

**Treating Sepsis in the “Golden Hour”**

Rapid initiation of simple, timely interventions including source control, appropriate antimicrobials, judicious intravenous fluids and targeted treatment to restore the circulation can halve the risk of dying.

**World Sepsis Day**

**September 13**

Dr Marc Ziegenfuss – Director AICS TPCH, President ANZICS
Sepsis

a global burden

~ 27 000 000
people per year develop sepsis

~ 19 000 000
people per year survive

~ 8 000 000
people per year die

Survivors may face lifelong complications
Global burden of sepsis: a systematic review
C Fleischmann, A Scherag, NK Adhikari, CS Hartog, T Tsaganos, P Schlattmann, DC Angus, K Reinhart
Critical Care 2015 19(Suppl 1):P21

- Sepsis is a global healthcare challenge. However, comprehensive information on sepsis morbidity and mortality across the world is scarce.

The term sepsis was introduced by Hippocrates in the fourth century BC, and it meant the process of decay or decomposition of organic matter.
Global Burden of Disease Study 2016

Lancet, The
Volume 390, Issue 10100
2017-09-16
Australian Sepsis Epidemiology

• incidence adult Australian population treated in ICU estimated at 0.77/1000; more than 15700 new cases each year; cost per episode of AUD39300.

• This estimate does not include patients not treated in an ICU and total number may be three or four times higher. As in excess of 3000 people die of sepsis in Australia each year, the burden of death from sepsis is greater than the annual national road toll and sepsis causes more deaths than breast, prostate or colorectal cancer.

• Yes, it affects YOU
### ICU Admission Sepsis Data based on ANZ

<table>
<thead>
<tr>
<th>Hospital Classification</th>
<th>Time Period</th>
<th>Admissions</th>
<th>ANZROD SMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANZ</td>
<td>5 year</td>
<td>40784</td>
<td>1.025</td>
</tr>
<tr>
<td>ANZ</td>
<td>1 year</td>
<td>10892</td>
<td>0.931</td>
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<tr>
<td>Rural</td>
<td>5 year</td>
<td>8000</td>
<td>0.934</td>
</tr>
<tr>
<td>Rural</td>
<td>1 year</td>
<td>2118</td>
<td>0.755</td>
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<tr>
<td>Metropolitan</td>
<td>5 year</td>
<td>11292</td>
<td>1.047</td>
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<tr>
<td>Metropolitan</td>
<td>1 year</td>
<td>3075</td>
<td>0.851</td>
</tr>
<tr>
<td>Tertiary</td>
<td>5 year</td>
<td>17949</td>
<td>1.027</td>
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<tr>
<td>Tertiary</td>
<td>1 year</td>
<td>4730</td>
<td>1.016</td>
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<tr>
<td>Private</td>
<td>5 year</td>
<td>3543</td>
<td>1.137</td>
</tr>
<tr>
<td>Private</td>
<td>1 year</td>
<td>1698</td>
<td>1.030</td>
</tr>
</tbody>
</table>

Fighting sepsis in Australia - “Sepsis Summit” roundtable
- The George Institute for Global Health
5 Year Sepsis Data based on all ANZ

ANZROD SMR
(new improved benchmarking model based on APACHE III-J)

APACHE III-J SMR
Challenges of Sepsis prevention

How long is a piece of string?
How much Time do we have?

-Famine, Trauma, clean water, poverty, overcrowding, easy access to effective healthcare, vaccination programs, vector controls, etc.
Hospital Beds

Hospital beds include beds in public and private hospitals, specialised hospitals, and rehabilitation centres. In 2002 there were an estimated 19.6 million hospital beds in the world. China, Japan and the Russian Federation are where the most hospital beds can be found. The most beds per person are found in Monaco, then Switzerland. There is one hospital bed for every 46 people living in Monaco, and one for every 56 people in Switzerland. In Niger there is just over one hospital bed for every 10000 people living there.
Poor water

Drinking water is essential to live, but dirty drinking water is also a major cause of disease. Whilst most people living in Western Europe can access safe water, only 50% of people living in Central Africa can do this. The largest population without access to safe tap water is in China: that is 324 million people, or 25% of the population. In a quarter of all territories more than a quarter of the population is without access to safe water. Worldwide 18% of people have no safe drinking water. Safer water can be obtained by treating water, collecting it from a spring, or pumping it up from groundwater.
Malnutrition... Prevention is better than cure

MAYBE THIS IS WHY KIDS ARE OBESE

Learn more about our project @ eatlocalgrown.com
Overcrowding

Overcrowding is defined here as when there are more than two people for each room in the house. The populations of richer territories experience less overcrowding, than those in poorer territories. Living in large groups is also connected to social and cultural norms. In India 77% of the population live in conditions that are considered to be overcrowded. Large proportions of the populations of other Southern Asian territories also live in overcrowded conditions: the Pakistan rate is 72%; Bangladesh is 61%; and Nepal is 48%.
Population Growth

[Graph showing world population growth from 1950 to 2050, with the x-axis representing years and the y-axis representing population in billions.]

[Map of the world with population cartograms showing the distribution of population across different regions.]
Ageing: The Sepsis Tsunami awaits....
“One should judge a community by how it treats its least fortunate”

- Ziegenfuss, Marc

Journal of Critical Care, Volume 30, Issue 6, 1403

“The Standard you walk past is the Standard you accept”.

- D Hurley
Progress ...

“\textit{It always seems impossible, until it is done.}”

– N Mandela

\textit{On Friday, May 26th, 2017, the World Health Assembly and the World Health Organization made sepsis a global health priority, by adopting a resolution to improve, prevent, diagnose, and manage sepsis. This marks a quantum leap in the global fight against sepsis.}
WHO Resolution outline

- Sepsis prevention, diagnosis & treatment
- Reduce Antimicrobial resistance – Antibiotics
- Optimal care pathways
- Public awareness for at risk population
- ICD coding

**TOP 10 risk factors for disease in 2010**

1. Household air pollution from solid fuels
2. Smoking/secondhand smoke
3. High blood pressure
4. Iron deficiency
5. Alcohol use
6. High plasma glucose
7. Suboptimal breastfeeding
8. Pollution
9. Childhood underweight
10. Low fruit intake

**Top killers across the world**

- High blood pressure
- Household air pollution from solid fuels
- High body mass index
- High fasting plasma glucose
- Air pollution
- High cholesterol
- Low bone mineral density

**Death due to dietary risk factors**

Disease attributable to tobacco smoking—63 | Alcohol and drug use—49 | Low diet of fruits—49 | High sodium diet—49 | Low nuts, seeds diet—25 | Low vegetable food—18 | Occupational risk factors accounted—25.4

**Know your Sepsis Six.**

1. Give high-flow oxygen
2. Take blood cultures
3. Give IV antibiotics
4. Give a fluid challenge
5. Measure lactate
6. Measure urine output

By doing these six simple things in the first hour, you can double your patient’s chance of survival.

**ICD-10 sepsis codes for the identification of sepsis cases in DRG statistics**

- Case identification—sepsis:
  - A69.1 (S aureus sepsis)
  - A69.2 (S pneumoniae sepsis)
  - A69.3 (Serratia marcescens sepsis)
  - A69.4 (Klebsiella pneumoniae sepsis)
  - A69.5 (Protozoan sepsis)

- Case identification—severe sepsis:
  - A69.1 (S aureus sepsis)
  - R56.1 (SIRS of infectious origin with organ failure)
  - R56.2 (SIRS of infectious origin with organ failure)
A systematic review and meta-analysis of early goal-directed therapy for septic shock: the ARISE, ProCESS and ProMISe Investigators

A Primary mortality outcome of each study

<table>
<thead>
<tr>
<th>Study</th>
<th>Events,</th>
<th>Events,</th>
<th>OR (95% CI)</th>
<th>EGDT</th>
<th>control</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivers et al. (2001)</td>
<td>38/130</td>
<td>59/133</td>
<td>0.52 (0.31, 0.86)</td>
<td></td>
<td></td>
<td>10.40</td>
</tr>
<tr>
<td>Jones et al. (2010)</td>
<td>34/150</td>
<td>25/150</td>
<td>1.47 (0.82, 2.60)</td>
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<td></td>
<td>4.87</td>
</tr>
<tr>
<td>ProCESS Investigators (2014)</td>
<td>92/439</td>
<td>167/902</td>
<td>1.17 (0.88, 1.55)</td>
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<td>21.78</td>
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<tr>
<td>ARISE Investigators (2014)</td>
<td>147/792</td>
<td>150/796</td>
<td>0.98 (0.76, 1.26)</td>
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<td></td>
<td>30.71</td>
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<tr>
<td>ProMISe Investigators (2015)</td>
<td>184/623</td>
<td>181/620</td>
<td>1.02 (0.80, 1.30)</td>
<td></td>
<td></td>
<td>32.23</td>
</tr>
<tr>
<td>Overall (I-squared = 56.7%, p = 0.055)</td>
<td>495/2134</td>
<td>582/2601</td>
<td>1.01 (0.88, 1.16)</td>
<td></td>
<td></td>
<td>100.00</td>
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</tbody>
</table>
The River’s work was useful....

• As it provided us a construct on how to understand resuscitation:
  – Start early- (give antibiotics)
  – Correct hypovolaemia
  – Restore perfusion pressure
  – And in some cases a little more may be required..!

• These concepts are as important today as they ever were.
Homo Deus
A Brief History of Tomorrow
Use of All Antibiotics in 2015

Source: IMS Health
THE SPREAD OF ANTIBIOTIC RESISTANCE
An increasing proportion of bacteria display resistance to common antibiotics.

*Enterobacteriae, including Escherichia coli, Klebsiella pneumonia, Enterobacter and Salmonella. Source: CDDEP ResistanceMap/IMS MIDAS
Superbugs and Super Risks: The Investment Case for Action: A briefing for investors

“From the farm to pharma, from livestock to life sciences, complacency in the administration of our invaluable antibiotics has led to dangerously high levels of antimicrobial resistance that risks wiping $100 trillion off potential global output by 2050.”

- Abigail Herron, Head of Responsible Investment Engagement, Aviva Investors
Deaths attributable to antimicrobial resistance every year by 2050

- North America: 317,000
- Latin America: 392,000
- Europe: 390,000
- Africa: 4,150,000
- Asia: 4,730,000
- Oceania: 22,000

Source: The Review on Antimicrobial Resistance
World Antibiotic Awareness Week, 13-19 November 2017

• The “Global action plan on antimicrobial resistance” has 5 strategic objectives:
  
  • To improve awareness and understanding of antimicrobial resistance.
  • To strengthen surveillance and research.
  • To reduce the incidence of infection.
  • To optimize the use of antimicrobial medicines.
  • To ensure sustainable investment in countering antimicrobial resistance.
Antimicrobial use & Livestock

Antimicrobial Consumption in Livestock
Estimates for 2010

Change in Antimicrobial Consumption in Livestock
Estimates for 2030

Center for Disease Dynamics, Economics & Policy (cddep.org) © Natural Earth
Antibiotic-Resistant Bacteria On:

- **81%** OF GROUND TURKEY
- **69%** OF PORK CHOPS
- **55%** OF GROUND BEEF
- **39%** OF CHICKEN BREASTS, WINGS AND THIGHS

*Based on EWG's 2013 report: Superbugs Invade American Supermarkets*

Biologische kip
930 gram

Plofkip
2,350 gram
World Antibiotic Awareness Week, 13-19 November 2017

• To prevent and control the spread of antibiotic resistance, the agriculture sector can:
  — Only give antibiotics to animals under veterinary supervision.
• Not use antibiotics for growth promotion or to prevent diseases.
• Vaccinate animals to reduce the need for antibiotics and use alternatives to antibiotics when available.
• Promote and apply good practices at all steps of production and processing of foods from animal and plant sources.
• Improve biosecurity on farms and prevent infections through improved hygiene and animal welfare.
Perceptions of communities and physicians in use of antibiotics

Q: Will you wish to change your doctor if he fails to prescribe antibiotics for your common cold?
A: 47% of patients said Yes

>>> But antibiotics cannot cure the common cold!

- Health in South-East Asia || March 2011
World Antibiotic Awareness Week, 13-19 November 2017

• To prevent and control the spread of antibiotic resistance, individuals can:

  • Only use antibiotics when prescribed by a certified health professional.
  • Never demand antibiotics if your health worker says you don’t need them.
  • Always follow your health worker’s advice when using antibiotics.
  • Never share or use leftover antibiotics.
  • Prevent infections by regularly by washing hands, preparing food hygienically, avoiding close contact with sick people, practising safer sex, and keeping vaccinations up to date.
Q: Would you prescribe antibiotics for your own use or that of your family members?
A: 53% of people would self-prescribe antibiotics
>>> Self-medication leads to antibiotic resistance

Q: Should antibiotics be discontinued by the patient when he starts feeling better, even before completion of recommended course?
A: 25% of responders said Yes
>>> But stopping antibiotics before the course is finished leads to antibiotic resistance.
To prevent and control the spread of antibiotic resistance, health professionals can:

- Prevent infections by ensuring your hands, instruments, and environment are clean.
- Only prescribe and dispense antibiotics when they are needed, according to current guidelines.
- Report antibiotic-resistant infections to surveillance teams.
- Talk to your patients about how to take antibiotics correctly, antibiotic resistance and the dangers of misuse.
- Talk to your patients about preventing infections (for example, vaccination, hand washing, safer sex, and covering nose and mouth when sneezing).
• Ageing, fragile population, prescribed a lot of antibiotics,
• High generational turnover facilitates mutation, natural selection and adaptation
• Modern medicine and human expectation of old age counter evolution of the innate immune system
• Should non-life threatening infection (in low risk groups) be treated with Antibiotics – ? at all ? vs when curable by other means eg. washing, I&D, secretion clearance, etc.
  – Patient expectation wrt Abs is a quick fix and symptom control

• How to manage “Anti-vaxers” ?
Responses to Sepsis – calling for Individual-specific Treatment, or not...

Immunosuppression in sepsis: a novel understanding of the disorder and a new therapeutic approach. Richard S Hotchkiss, MD, Guillaume Monneret, PhD, and Didier Payen, MD
More of this?

When not to treat an Infection with Antibiotics?

| Clinical assessment | Recurrent 
|---------------------|-----------------|

<table>
<thead>
<tr>
<th>2. Capacity assessment</th>
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<table>
<thead>
<tr>
<th>V</th>
<th>I believe that the patient has capacity* to consent to and/or refuse medical treatment.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>□ I believe that the patient does not have capacity to consent to and/or refuse medical treatment.</td>
</tr>
</tbody>
</table>

If there is a change in capacity, this form must be reviewed.

| Details of assessment: |

| 3. Resuscitation management plan |

If an acute deterioration or critical event occurs, it is clinically indicated to:

| Provide e.g. ventilation, IV fluids, supportive therapies |

| APPROPRIATE CARE |

| Not provide e.g. defibrillation, intubation, antibiotics |

| ANTIBIOTICS |

There is further documentation in the progress notes on the following dates: 18/9/2018

If a cardiac or respiratory arrest occurs, it is clinically appropriate to:

| CPR | Provide | Do not provide |

A decision not to provide CPR does not limit other treatment or care

If the Resuscitation management plan differs from the choices of the patient (see Section 4) regarding future medical treatment, record the details in the progress notes or on this form and follow an appropriate resolution process (see Section 4 in the Quick Guide).
ATUL GAWANDE

BEING MORTAL

Illness, Medicine, and What Matters in the End

“This is Atul Gawande’s most powerful, and moving, book.”
Malcolm Gladwell
“The best screening tools for sepsis remain **within the minds of clinicians**, suspecting infection and assessing organ function using an array of criteria that so far have eluded complete description.” Prof. Jean-Louis Vincent
Why we need awareness...

Sepsis Biomarker Time Course Following Pathogen Exposure

The ideal objective biomarker test for sepsis...

Fig. 5. Schematic representation of the considerations to be addressed in designing a real-time sepsis biomarker monitoring system. SPR, surface plasmon resonance; QCM, quartz crystal microgravimetry.
Nature Communications: "A point-of-care microfluidic biochip for quantification of CD64 expression from whole blood for sepsis stratification"
Examining genetic markers in sepsis

• With the failure of a ‘one size fits all’ approach, UQ researchers are collaborating with The George Institute for Global Health to create a genomic resource to help develop personalised treatment options for septic shock.


Funded by National Health and Medical Research Council
Managed by University of Queensland
Provided by National Health and Medical Research Council
Overview of differentially expressed genes between SRS groups involving HLA and T-cell activation

Red shading shows upregulation and green shading shows downregulation of genes (FC>1.5, FDR<0.05) for SRS1 versus SRS2. Solid lines show direct association, dashed lines show indirect association. SRS=sepsis response signature. FC=fold change. FDR=false discovery rate. MHC=major histocompatibility complex

Genomic landscape of the individual host response and outcomes in sepsis: a prospective cohort study. Emma E Davenport, DPhil,a Katie L Burnham, MGen,a,† Jayachandran Radhakrishnan, DPhil,a,† Peter Humburg, PhD,a Paula Hutton, PG Cert,b Tara C Mills, DPhil,a Anna Rautanen, PhD,a Anthony C Gordon, MD,c Christopher Garrard, DPhil,b Adrian V S Hill, Prof, DPhil,a Charles J Hinds, Prof, FRCP,d and Julian C Knight, Prof, DPhil,a,* Lancet Respir Med. 2016 Apr; 4(4): 259–271.
A METHODICAL APPROACH - SEPSIS

-- STAFF
-- ENVIRONMENT, EQUIPMENT
-- PATIENT, PROCESSES
-- STEWARDSHIP
-- INFECTIVE PATHOGENS
-- SURVEILLANCE

ALL OF WHICH CAN BE A CHALLENGE
Handwashing:

- is there a Problem?

- Find a relevant solution taking into account local resources, efforts & desired outcomes into account cf Haiti

- Appropriate timely intervention

- Hubris
Beyond hospital discharge …

The Lingering Consequences of Sepsis
A Hidden Public Health Disaster?

Derek C. Angus, MD, MPH

Sepsis, the syndrome of infection complicated by vital organ dysfunction, is a medical emergency that affects more than 750,000 patients in the United States each year and remains one of the world’s leading...
### The price for success?

#### Figure. Potential Mechanisms of Decreasing Short-term Mortality Among Patients Across a Distribution of Illness Severity

<table>
<thead>
<tr>
<th>Current care</th>
<th>Significant morbidity</th>
<th>Death</th>
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<tbody>
<tr>
<td>Full recovery</td>
<td></td>
<td></td>
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<tr>
<td>Alternative mechanisms of potentially decreasing short-term mortality</td>
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<td></td>
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<tr>
<td>A Overall improvement: more recovery, less morbidity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full recovery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B Change viability threshold: same recovery, more morbidity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full recovery</td>
<td></td>
<td></td>
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<tr>
<td>C Trade-off: less recovery, even more morbidity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full recovery</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Iwashyna and Angus JAMA 2014
What about the survivors?

Long-term Cognitive Impairment and Functional Disability Among Survivors of Severe Sepsis

Prevalence of moderate/severe cognitive impairment increased >10%

High rate of new functional impairments

Declines in cognitive/functional impairment persisted > 8 years
Neurocognitive defects

asked to copy above picture, results below:

Near normal rendition by unimpaired 69 y/o pulmonary embolus survivor

Moderate to severely impaired 89 y/o Pneumonia survivor

Severely impaired 72 y/o ARDS survivor

It’s not all Doom and Gloom...
Fast food giant McDonald’s has recently announced that it aims to serve up more antibiotic-free meat at its restaurants around the world.

McDonald’s has said that from 2018 it will begin implementing a new chicken antibiotics policy in markets around the world, which will require the elimination of antibiotics defined by the WHO as Highest Priority Critically Important ("HPCIA") to human medicine.

This plan includes Australia. McDonald’s estimate that each year it purchases 21.4 million kilos of Australian chicken.

The world’s largest burger chain will also work toward limiting the use in cattle and pigs of antibiotics important to human medicine, a significant move because McDonald’s is such a significant purchaser of beef and pork.

Antimicrobial resistance is the ability of a microorganism (like bacteria, viruses and parasites) to stop an antimicrobial (such as antibiotics, antivirals and antimalarials) from working against it.

As a result, standard medical treatments become ineffective, infections persist and may spread to others. Resistance to current antimicrobials is increasing faster than the development of new drugs, and so effective treatments cannot keep pace. The World Health Organization (WHO) describes AMR as a looming crisis in which common and treatable infections will become life threatening.

More than 1,000 cases of almost-untreatable superbugs were reported in Australia in the 12 months to March this year.

For the first time, the Australian Commission on Safety and Quality in Health Care has tracked dangerous bacteria resistant to the last line of antibiotics.

Speaking to SKY News earlier this year, AMA Vice President Dr Tony Bartone said: “The over-prescription of antibiotics is a problem because, world-wide, we’ve seen the emergence of what we call anti-microbial resistance – that is, resistance by bacteria to antibiotics, life-saving antibiotics in the past.

“Now with this emerging resistance, it’s becoming more and more difficult to treat these resistant bacteria, and we’ve all got a role to play in trying to reduce that incidence and that spread.”

In April 2014, WHO released its new global report, Antimicrobial resistance: global report on surveillance, which states ‘...this serious threat is no longer a prediction for the future, it is happening right now in every region of the world and has the potential to affect everyone.’

The Australian Government and other international governments have already identified antimicrobial resistance (AMR) as a high-priority issue.

MEREDITH HORNE

Don’t let her drink dirty water
malaria, typhoid, dysentery, cholera, diarrhoea, intestinal worm infection, ... dirty water can kill.

6,000 children are dying every day – and it’s because they don’t have clean water. So they’re forced to drink water that could make them sick with diarrhoea, cholera and typhoid.

The good news is, problems like dirty water can be solved. You can help children access clean water through World Vision's Water Health Life program by providing practical and effective solutions.

From $39 a month your support will help drill boreholes, protect water sources and provide health and hygiene training. You’ll be helping communities to make long-term changes that ensure a clean water supply and basic sanitation.

Stop dirty water killing children, support Water Health Life: visit worldvision.com.au or call 13 32 40.

Water Health Life
Basic Needs: Permanent Solutions

World Vision, a Christian organisation, partners with local churches, whose work and witness are recognised in the world.

ABN 36 088 914 909 | ACN 130 054 432 |
Reaching out for Sepsis awareness...

Figure 1. World Mobile and Internet Penetration Rates

The world map of social networks

Mobile Growth Continues Through 2020
By 2020, more people will have mobile phones than electricity at home

- People with mobile phones: 5.4 billion
- People with electricity: 5.3 billion
- People with bank accounts: 4.5 billion
- People with running water: 3.5 billion
- People with cars: 2.6 billion
- People with landlines: 2.2 billion

Source: 2009 World Factbook, Central Intelligence Agency © CIA 2009
“Be the change you want to see in the World.”

– M. Gandhi

“Every Flood starts with a single Raindrop. Be that Raindrop”

- Marc Ziegenfuss, Sydney, 29 September 2017