Intensive care unit mobility practices in Australia and New Zealand: a point prevalence study

Immobility, deconditioning and muscle weakness are a consequence of critical illness. This results in longstanding impaired physical function for survivors of intensive care.^{1,2} Early mobilisation for patients who are intubated and receiving mechanical ventilation in the intensive care unit is advocated as a treatment intervention that may attenuate the development of weakness.³⁻⁶ To date, several cohort studies have shown that early mobilisation for these patients is feasible and safe,⁶⁻⁸ and is associated with a reduction in ICU length of stay, hospital length of stay⁶ and hospital readmission up to 1 year after discharge.⁹ There are few large randomised controlled trials showing the effects of early mobilisation on patient-centred outcomes.

Survey data suggest that physiotherapists incorporate mobilisation as part of their clinical practice in the ICU.¹⁰ No widespread prospective audit of mobilisation in the ICU has occurred in Australia or New Zealand. Our aim was to document current physiotherapy mobilisation practices across a large sample of general (medical and surgical) ICU patients and focus specifically on mobilisation practices in patients requiring prolonged mechanical ventilation, defined as more than 48 hours.

Methods

Sites and ethics approval

Our study was conducted within the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG) point prevalence program and was endorsed by the ANZICS CTG. All ICUs in Australia and New Zealand were invited to participate. The point prevalence program is a mechanism to conduct multiple prospective one-day observational epidemiological studies and was approved by the appropriate institutional, state or national multicentre ethics committee for each participating hospital, with the need for participant consent waived. Data were de-identified before submission to the coordinating centre.

Survey

Our study was performed in each site on one of three designated days in 2009 and 2010. A 30-item general case report form (CRF) was completed by a research nurse, and a 25-item physiotherapy-specific CRF was completed by a research nurse or physiotherapist. The physiotherapy CRF

Susan C Berney, Megan Harrold, Steven A Webb, Ian Seppelt, Shane Patman, Peter J Thomas and Linda Denehy

ABSTRACT

Objectives: To develop a comprehensive set of items describing physiotherapy mobilisation practices for critically ill patients, and to document current practices in intensive care units in Australia and New Zealand, focusing on patients having > 48 hours of mechanical ventilation.

Design: Prospective, observational, multicentre, single-day, point prevalence study.

Participants and setting: All patients in 38 Australian and New Zealand ICUs at 10 am on one of three designated days in 2009 and 2010.

Main outcome measures: Demographic data, admission diagnosis and mobilisation practices that had occurred in the previous 24 hours.

Results: 514 patients were enrolled, with 498 complete datasets. Mean age was 59.2 years (SD, 16.7 years) and 45% were mechanically ventilated. Mobilisation activities were classified into five categories that were not mutually exclusive: 140 patients (28%) completed an in-bed exercise regimen, 93 (19%) sat over the side of the bed, 182 (37%) sat out of bed, 124 (25%) stood and 89 (18%) walked. Predefined adverse events occurred on 24 occasions (5%). No patient requiring mechanical ventilation sat out of bed or walked. On the study day, 391 patients had been in ICU for > 48 hours. There were 384 complete datasets available for analysis and, of these, 332 patients (86%) were not walked. Of those not walked, 76 (23%) were in the ICU for \geq 7 days.

Conclusion: Patient mobilisation was shown to be low in a single-day point prevalence study. Future observational studies are required to confirm the results.

Crit Care Resusc 2013; 15: 260–265

consisted of two items about service provision, two about respiratory care, 10 about mobilisation practices (including respiratory support and barriers to mobilisation), 11 items about factors interfering with physiotherapy (such as renal replacement therapy or procedures outside the ICU), and two items about unplanned or adverse events occurring during physiotherapy. The survey questions are available from the author.

Table 1. Safety assessment for patient mobilisation, using selected elements of the SOFA score¹¹ and RASS¹² for patients with an ICU LOS > 48 hours

Characteristic	Measurement				
SOFA score	0	1	2		
PaO ₂ /FIO ₂	>400	301–400	201–300;* <301 [†]		
Cardiovascular parameters	MAP > 70 mmHg	MAP < 70 mmHg	Dopamine ≥ 5 μg/ kg/min [‡]		
RASS	-1	0	1		
Assessment	Drowsy§	Alert, calm	Restless [¶]		
SOFA = sequential organ failure assessment. RASS = Richmond agitation and sedation score. ICU = intensive care unit. LOS = length of stay. MAP = mean arterial pressure. * With respiratory support. † Without respiratory support. ‡ Or any dose of dobutamine, milrinone or levosimendan. § Not fully alert but sustained (10-second) awakenings with eye contact to voice. ¶ Anxious or apprehensive, movements not aggressive or vigorous.					

Data on all mobility and rehabilitation activities undertaken by patients in the previous 24 hours were collected from the nursing or physiotherapy notes, or from the daily observation chart. Each activity was predefined, using a data dictionary. Mobilisation activities included in-bed exercise activity, sitting in bed or sitting out of bed, and all walking that occurred. "Walking" was defined as taking three steps on the spot or away from the bedside.

Patients

All adult patients (aged 16 years or over) who were admitted to the ICU at a 10 am census point on the designated day were included. Demographic data including age, sex and admission diagnosis were recorded. Admission diagnoses were categorised by the Acute Physiological and Chronic Health Evaluation (APACHE) II score in the 24 hours before the study day, and according to whether the patient

was admitted to or discharged from the ICU on the study day. A subset of patients in the ICU for more than 48 hours was analysed separately to determine the prevalence of early mobilisation in patients with prolonged stays in the ICU.

Safety criteria

Safety criteria were developed and defined by five of us (four of whom had over 10 years' clinical ICU experience): two senior ICU staff specialists and three experienced ICU physiotherapists. Criteria were developed using available data from the general section of the CRF, and were based on parameters used in clinical trials that had examined ICU patient mobilisation and on two of our Australian trials that were then underway. These criteria were presented to the ANZICS CTG in 2009 and agreed on by senior medical, nursing and physiotherapy clinicians present. The definitions of these criteria are shown in Table 1.

We retrospectively applied the safety criteria using the Richmond agitation and sedation score (RASS) and the respiratory and cardiovascular components of the sequential organ failure assessment (SOFA) score to each patient, and classified patients as safe or unsafe to mobilise. We used these safety criteria to investigate if consistent safety criteria were used in the decision to sit patients out of bed or walk them away from the bed, and to determine if there was potential for greater levels of mobilisation.

Analysis

Statistical analysis was performed using SAS version 9.1 (SAS Institute). Variables that were normally distributed were reported as means with standard deviations, and non-normally distributed data were reported as medians with interquartile ranges. Proportions were reported as percentages.

Results

ICU and patient data

Thirty-eight units participated in the point prevalence study (33 in Australia and five in New Zealand). All were closed multidisciplinary ICUs, with patient management supervised by accredited ICU specialists. There are 182 ICUs in Australia and New Zealand. The sample from our study represented 30 of 35 tertiary units in Australia and New Zealand (86%), six of 39 metropolitan units (15%), one of 49 rural and regional units (2%), and one of 59 private hospital units (2%).



Table 2.	Demographic	data of ICU	patients
----------	-------------	-------------	----------

Characteristic	n (%)*	
Mean age, years ($n = 504$)		
20–59	219 (43%)	
60–79	236 (47%)	
> 80	49 (10%)	
Overall mean 59.2 years; SD, 16.7 years		
Weight, kg (<i>n</i> = 513)		
< 70	150 (29%)	
70–100	294 (57%)	
> 100	69 (13%)	
APACHE II ($n = 480$) score		
< 10	53 (11%)	
10–20	232 (48%)	
21–29	149 (31%)	
≥ 30	46 (10%)	
Source of ICU admission ($n = 514$)		
Emergency department	133 (26%)	
Elective surgery	127 (25%)	
Emergency surgery	86 (17%)	
Other	168 (33%)	
Reason for ICU admission ($n = 465$)		
Postoperative care	213 (46%)	
Sepsis	123 (26%)	
Trauma	77 (17%)	
ALI	26 (6%)	
ARDS	26 (6%)	
Length of ICU stay, days $(n = 419)$		
<2	177 (42%)	
2–7	106 (25%)	
>7	136 (32%)	

ICU = intensive care unit. ALI = acute lung injury. ARDS = acute respiratory distress syndrome. APACHE = Acute Physiology and Chronic Health Evaluation. * Percentages may not total 100 due to rounding.

Data were collected on 514 patients who had spent any time in the ICU after 10 am on the study day. Of the 514 patients, 16 had some missing data. Of the remaining 498 patients, 222 (45%) were receiving mechanical ventilatory support and 276 (55%) patients were breathing spontaneously with oxygenation but not ventilatory assistance (Figure 1). The demographic data for the cohort are shown in Table 2. For 90% of patients, this was their first ICU admission during that hospital stay.



Mobilisation activities

Mobilisation activities of all 498 patients were classified into five categories that were not mutually exclusive: 140 (28%) completed an in-bed exercise regimen; 93 (19%) sat over the side of the bed; 182 (37%) sat out of bed; 124 (25%) stood and 89 (18%) walked.

Predefined adverse events occurred on 24 occasions (5%). No serious adverse event occurred resulting in death, cardiac or respiratory arrest or a patient fall. Of the 24 adverse events recorded, patients were returned to bed on seven occasions (30%) because of a reduction in mean arterial blood pressure. On six occasions (25%), the patient required an increase in positive end-expiratory pressure (PEEP) to > 10 cmH₂O, or > 20% increase in PEEP if already $> 10 \text{ cmH}_2\text{O}$. The remaining 11 adverse events included arrhythmia, bronchospasm and deterioration in mental state. No loss of airway or intravascular line occurred during mobilisation exercises. Physiotherapists were involved in mobilisation activities, including sitting out of bed, on 90% of occasions.



Figure 3. Frequency of mobilisation activities undertaken by patients in

Table 3. Main reasons for not sitting out of bed or walking

Reason	Not sitting out of bed <i>n</i> (%)	Not walking <i>n</i> (%)	
Unconscious or unresponsive	49 (20%)	5 (7%)	
Sedated or agitated	42 (17%)	NA	
No RASS recorded	5	NA	
RASS recorded	37	NA	
RASS –1 to –3	22	NA	
RASS <-4	11	NA	
RASS > 0	4	NA	
No stated barrier	33 (13.4%)	31 (41%)	
Haemodynamic instability	28 (11.4%)	NA	
No inotropic support detailed	23	NA	
Weakness	23 (9.4%)	22 (29%)	
Unstable trauma	11 (4.5%)	2 (3%)	
Severe respiratory failure	11 (4.5%)	NA	
With ARDS	2	NA	
No ARDS or ALI	9	NA	
Renal replacement therapy	8 (3.3%)	NA	
Femoral access	2	NA	
Subclavian or jugular access	6	NA	

RASS = Richmond agitation and sedation score. ARDS = acute

respiratory distress syndrome. ALI = acute lung injury.

Respiratory support during out-of-bed mobilisation

No patients on mechanical ventilation were sat out of bed or walked. Twenty patients with artificial airways, but not mechanical ventilation, were mobilised out of bed. Two of the 20 patients had an endotracheal tube in situ and were sat out of bed, and one was mobilised; both patients were on T-piece oxygenation at the time. Eighteen patients with a tracheostomy tube in situ were sat out of bed, and eight of these were also mobilised. One hundred and fifty patients (30%) were mobilised on face mask oxygen, and one was mobilised while receiving non-invasive ventilation. On 10 occasions, respiratory support was not recorded.

Out-of-bed mobilisation for patients in the ICU > 48 hours

All further results pertain to a subgroup of the original 514 patients, the 391 patients (76%) who were in the ICU > 48 hours. Seven had missing data, and of the 384 complete data sets, 200 (52%) were receiving mechanical ventilatory support. The ventilatory status of these patients is given in Figure 2.

The numbers of patients undertaking different mobilisation activities are shown in Figure 3. Of the 384 patients, 332 (86%) were not walked. Of these 332 patients, 76

Table 4. Safety criteria for sitting out of bed

	Sat out of bed		Walked	
Criterion	Yes	No	Yes	No
Within SOFA and RASS parameters (n = 125*)	69	56	30	93 (88) [†]
Not within SOFA and RASS parameters (<i>n</i> = 266*)	59	207	22	245
Total	128	263	52	388
COEA		L DAGG	D' 1	1 1 1

SOFA = sequential organ failure assessment. RASS = Richmond agitation and sedation score. * SOFA parameters: cardiovascular 0–2, respiratory 0–2; RASS parameters: 1 to –1 (1 = restless, anxious, movements not aggressive; 0 = alert, calm; –1 = drowsy, not fully alert but has sustained awakenings). † Due to trauma such as spinal cord injury and stroke in five patients, only 88 patients were potentially able to walk.

(23%) were in the ICU for 7 days or longer. All predefined adverse events previously described occurred in this longerstay cohort of patients. Similarly to what was observed in the entire cohort, physiotherapists performed mobilisation activities on 81% of occasions.

Of the 150 patients receiving oxygen therapy via a face mask, 85 (57%) sat out of bed and 45 (30%) walked. All previously described out-of-bed mobilisation activities for patients with an artificial airway in situ occurred in patients whose length of stay in ICU was > 48 hours.

The barriers to sitting patients out of bed and/or walking them were reported by the clinical staff caring for the patients and are shown in Table 3.

Application of objective safety criteria

Of the 384 patients with a length of stay >48 hours and complete datasets (Figure 2), 125 patients (33%) met the predefined safety criteria to sit out of bed and walk (Table 4). Sixty-nine sat out of bed and 30 walked.

Of the 266 patients (68%) who did not meet the predefined safety criteria, 59 sat out of bed, and 22 of those 59 walked. On 58 occasions, the patient did not meet the respiratory criteria, and on one occasion, the patient did not meet the cardiovascular criteria. On one occasion, mobilisation occurred when the patient did not meet the respiratory and RASS safety criteria, and on all other occasions one safety criterion was not met. No patient who sat out of bed or was mobilised when they did not meet the safety criteria experienced an adverse event.

On 73 occasions, patients had a procedure in the ICU or were transported outside the ICU, and these procedures may have interfered with mobilisation in the 24 hours of data collection. Thirty-eight of these occasions (52%) were associated with imaging, which on three occasions resulted in a surgical procedure being performed in the ICU. On 16 occasions (22%), patients underwent surgical procedures in the operating room. On 11 occasions (15%), these patients were sat out of bed or mobilised, and on 15 occasions (21%) these patients met safety criteria but were not mobilised.

Discussion

Recent evidence suggests that survivors of intensive care may suffer longstanding muscle weakness.^{1,13} Early mobilisation, particularly walking, that begins in the ICU in patients who are intubated and ventilated is advocated as a treatment intervention to attenuate muscle weakness and improve patient outcomes.^{3,6,14} The results of our point prevalence study indicate that critically ill patients in Australia and New Zealand perform a range of mobilisation activities either in bed or sitting out in a chair. However, only 18% of all patients in the ICU walked and, for those staying in the ICU for >48 hours, this decreased to 13%. No patient requiring mechanical ventilation either sat out of bed or walked on the day of our study.

This was a mixed medical and surgical cohort, and about 40% of patients were postoperative. We were most interested in physiotherapy practices for patients admitted for > 48 hours, rather than for patients admitted for routine postoperative surveillance who were likely to be discharged within 24 hours. Physiotherapists in Australia and New Zealand are part of the multidisciplinary team. They provide respiratory care and rehabilitation for patients in the ICU. Most ICUs in Australia have at least one physiotherapist on staff, with half the therapists having >5 years of clinical experience in intensive care.^{10,15} No data describing the profile of physiotherapists in New Zealand ICUs has been published but we would expect it to be similar.

Self-reporting surveys of physiotherapists working in the critical care setting have described the provision of mobilisation practices.^{10,16-18} A survey by Skinner and colleagues of Australian mobility practices in ICUs reported that 94% of physiotherapists would routinely prescribe mobilisation exercise for patients.¹⁰ That survey of 111 physiotherapists reported that 103 respondents (93%) would prescribe inbed mobilisation exercises, 100 (90%) would sit patients over the edge of the bed, and over 100 (90%) would walk patients on the spot or away from the bed. Skinner and colleagues also reported that, in patients who were mechanically ventilated, 56 of 102 physiotherapists (55%) would mobilise the patient away from the bed. Our results do not support those results, with fewer than 50% of patients in our study having received any form of mobilisation activity.

United Kingdom survey data reported similar findings to those of Skinner and colleagues, with almost all physiotherapists surveyed stating that they provide mobilisation exercises in the ICU. These results may highlight potential issues with self-reporting surveys compared with prospective data. To date, no prospective data are available to compare physiotherapy practices in the UK.

The results of this study reflect a lack of consensus on safety criteria for mobilising patients, particularly for sitting out them of bed and walking them, in ICUs across Australia and New Zealand. This was reflected by the number of patients who did not meet our predefined safety criteria and who sat out of bed (46%) and walked (42%). While there was broad agreement about which patients were not safe to sit out of bed or walk, there was little agreement about who was safe to mobilise out of bed. In our study, using our safety criteria, 15% more patients could have sat out of bed and 36% more could have walked. This is despite the low rate of adverse events reported in our study and in the literature on early mobilisation of patients in the ICU.^{6,7,19} The low rate of adverse events reported in our study is consistent with other studies of functional mobility practices in the critical care setting, with reported rates between 0% and 5%.^{6,8,19}

An alternative explanation for our low observed rates of ICU patients sitting out of bed and walking may be that we have not yet developed a culture of early mobility across Australia and New Zealand. Haemodynamic instability was reported on 28 occasions as a reason for the patient not to sit out of bed, but 23 of these patients were not receiving inotropic support. On 45 of the 76 occasions that patients were not walked once they were sitting in the chair, no reason was given for why they were not walked. These barriers may reflect a reluctance of staff to engage in early mobilisation of patients who are critically ill, and there may be many variables that have an impact on ICU mobilisation practices.

A solution may be to develop stepwise protocols that prescribe mobilisation activity based on the cognitive level and physical capacity of the patient. Protocols such as these have been safely and effectively introduced into clinical practice.⁶ In one centre in the United States, they have resulted in patients walking at least 3 days sooner, an adverse event occurrence of <1% and an increase in mobility of up to twofold.⁶ In another US centre, an increase in routine mobilisation occurred.¹⁹

Patients were unavailable for part of the 24 hours of data collection on 73 occasions. While we acknowledge that some of the procedures affecting our data collection, such as surgical interventions in the operating theatre, may have had an impact on ICU patient mobilisation, they were not common enough to influence the overall results of our study.

Limitations

There are several limitations to our study. Point prevalence data may not be representative of usual practice, but in this study we documented all mobilisation in the previous 24 hours, not just what had occurred at a single time on the study day. Prevalence data (compared with incidence data) can be biased in favour of long-term patients, but in our study this was precisely our group of interest, and even with this bias, our observed number of mobilisation episodes was low.

At different sites, physiotherapists and research nurses carried out the data collection, and the variation in training of these two professions may introduce bias in the reporting. There were also missing data in the cases, which changes the sample size for different responses. This may also introduce bias in results. The pragmatic safety criteria that were applied to the data retrospectively to determine if further mobilisation may have been possible were not comprehensive. We were limited to information already collected as part of the point prevalence survey and, although based on safety criteria used in trials of early mobilisation, we acknowledge that other potentially important factors may have contributed to the observed rates of mobilisation.

Conclusion

On a single day in 38 ICUs in Australia and New Zealand, the number of patients mobilised was low, and much lower than predicted by our prespecified safety criteria and previous selfreported descriptions of practice. By restricting a patient's capacity to sit out of bed and walk, we may be limiting their functional recovery. A further program of research starting with a prospective observational study is required to confirm these data. We are awaiting similar audit data to compare our results with international ICU cohorts.

Competing interests

None declared.

Author details

Susan C Berney, Associate Professor,¹ and Physiotherapy Manager² Megan Harrold, Lecturer,³ and Senior Physiotherapist⁴

Steven A Webb, Senior Staff Specialist,⁴ and Clinical Professor, School of Medicine and Pharmacology⁵

Ian Seppelt, Senior Staff Specialist, $^{\rm 6}$ Director of Clinical Research, $^{\rm 7}$ and Senior Research Fellow $^{\rm 8}$

Shane Patman, Associate Professor,⁹ and Senior Physiotherapist¹⁰

Peter J Thomas, Senior Physiotherapist¹¹

Linda Denehy, Head¹

- 1 Department of Physiotherapy, School of Health Sciences, University of Melbourne, Melbourne, VIC, Australia.
- 2 Austin Health, Melbourne, VIC, Australia.
- 3 Curtin University, Perth, WA, Australia.
- 4 Royal Perth Hospital, Perth, WA, Australia.
- 5 University of Western Australia, Perth, WA, Australia.
- 6 Intensive Care Medicine, Nepean Hospital, Sydney, NSW, Australia.
- 7 Sydney West Area Health Service, Sydney, NSW, Australia.

- 8 The George Institute for Global Health, Sydney, NSW, Australia.
- 9 School of Physiotherapy, University of Notre Dame, Perth, WA, Australia.
- 10 Fremantle Hospital and Health Service, Perth, WA, Australia.
- 11 Royal Brisbane and Women's Hospital, Brisbane, QLD, Australia.
- Correspondence: I.denehy@unimelb.edu.au

References

- 1 Cuthbertson BH, Roughton S, Jenkinson D, et al. Quality of life in the five years after intensive care: a cohort study. *Crit Care* 2010; 14: R6.
- 2 Herridge MS, Tansey CM, Matté A, et al. Functional disability 5 years after acute respiratory distress syndrome. *N Engl J Med* 2011; 364: 1293-304.
- 3 Needham DM. Mobilizing patients in the intensive care unit: improving neuromuscular weakness and physical function. *JAMA* 2008; 300: 1685-90.
- 4 Needham DM, Korupolu R, Zanni JM, et al. Early physical medicine and rehabilitation for patients with acute respiratory failure: a quality improvement project. *Arch Phys Med Rehabil* 2010; 91: 536-42.
- 5 Morris PE, Herridge MS. Early intensive care unit mobility: future directions. *Crit Care Clin* 2007; 23: 97-100.
- 6 Morris PE, Goad A, Thompson C, et al. Early intensive care unit mobility therapy in the treatment of acute respiratory failure. *Crit Care Med* 2008; 36: 2238-43.
- 7 Bailey P, Thomsen GE, Spuhler VJ, et al. Early activity is feasible and safe in respiratory failure patients. *Crit Care Med* 2007; 35: 139-45.
- 8 Thomsen GE, Snow GL, Rodriguez L, Hopkins RO. Patients with respiratory failure increase ambulation after transfer to an intensive care unit where early activity is a priority. *Crit Care Med* 2008; 36: 1119-24.
- 9 Morris PE, Griffin L, Berry M, et al. Receiving early mobility during an intensive care unit admission is a predictor of improved outcomes in acute respiratory failure. *Am J Med Sci* 2011; 341: 373-7.
- 10 Skinner EH, Berney S, Warrillow S, Denehy L. Rehabilitation and exercise prescription in Australian intensive care units. *Physiotherapy* 2008; 94: 220-9. doi: 10.1016/j.physio.2007.11.004.
- 11 Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/ failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med* 1996; 22: 707-10.
- 12 Sessler CN, Grap MJ, Brophy GM. Multidisciplinary management of sedation and analgesia in critical care. *Semin Respir Crit Care Med* 2001; 22: 211-26.
- 13 Needham DM, Davidson J, Cohen H, et al. Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. *Crit Care Med* 2012; 40: 502-9.
- 14 Schweickert WD, Kress JP. Implementing early mobilization interventions in mechanically ventilated patients in the ICU. *Chest* 2011; 140: 1612-7.
- 15 Wiles L, Stiller K. Passive limb movements for patients in an intensive care unit: a survey of physiotherapy practice in Australia. *J Crit Care* 2010; 25: 501-8.
- 16 Nava S. Rehabilitation of patients admitted to a respiratory intensive care unit. Arch Phys Med Rehabil 1998; 79: 849-54.
- 17 Lewis M. Intensive care unit rehabilitation within the United Kingdom: review. *Physiotherapy* 2003; 89: 531-8.
- 18 Norrenberg M, Vincent JL. A profile of European intensive care physiotherapists. European Society of Intensive Care Medicine. *Intensive Care Med* 2000; 26: 988-94.
- 19 Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet* 2009; 373: 1874-82.