strengthened. If recommendations were to support use of the vaccine with booster in the 5–17 months age range, at least two new visits for immunisation and a new visit for the booster would be needed.

Malaria remains an ongoing public health crisis in many settings in sub-Saharan Africa. Every day, on average, about 1200 children die in sub-Saharan Africa from malaria.[5] This figure is a substantial reduction from mortality estimates 15 years ago, and the decline has been associated with scale-up in longlasting insecticidal nets, access to effective artemisinin-combination treatments, and other WHO recommended control measures. Nevertheless, present mortality owing to malaria is unacceptable. Drug and insecticide resistance are major threats, and new malaria interventions are necessary.

The donor community would need to coordinate any financing for the RTS,S/AS01 vaccine carefully, should it reach that stage. In particular, funding must not be redirected away from meeting adequate access to artemisinin-combination treatments, rapid diagnostic tests, longlasting insecticidal nets, and other malaria control measures already in place in some settings, and financial resources might be better raised through the GAVI Alliance, if their board chooses to support such a role. GAVI has a strong track record for financing the delivery of new vaccines in sub-Saharan Africa. Finally, strong guidance is needed about the role of the vaccine in the context of existing malaria control measures, and about which malaria transmission intensity settings are best suited for vaccine use. The outcomes of regulatory and global policy assessments will no doubt be of interest to policy makers in malaria-endemic countries and multilateral financing agencies. WHO has a major responsibility to articulate evidence-based policy recommendations for use to support decision making in malaria-endemic countries.

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AVERT: a major milestone in stroke research

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See Articles page 46

Prevention of stroke is, of course, the ideal scenario, but with more than 10 million major strokes every year worldwide, acute treatment and rehabilitation should also be optimised. Organised acute stroke care within dedicated stroke units reduces death and dependency after stroke,[1] but which elements of such care confer this benefit is uncertain. Systematic prevention of common complications and more expert nursing care undoubtedly contribute, but in the physiologically unstable setting of acute stroke, the benefits and harms of each specific element of care need to be reliably assessed.

How soon and how intensively patients with acute stroke should be mobilised is an obviously important question. Early mobilisation after stroke, whether sitting, standing, or walking, is recommended in many guidelines, but, as with most nursing and therapist interventions, the evidence base has been weak. The rationale for early and more intensive mobilisation is that bed rest might increase immobility-related complications and could slow neurological recovery by impairing early brain plasticity and repair. On the other hand, forced sitting and standing might lead to falls and injury and could reduce cerebral perfusion, autoregulation being impaired in acute stroke, and thereby exacerbate ischaemia. Early mobilisation might also worsen any post-stroke hypertension and increase the risk of rebleeding after intracerebral haemorrhage or after thrombolysis for ischaemic stroke.

In *The Lancet*, the AVERT Collaboration group randomly assigned 2104 patients within 24 h of onset of acute stroke to early mobilisation or usual care.[2]


Thomas Fredberg/Science Photo Library

The intervention tested was not simply earlier, but was also more frequent and of a higher dose than usual care. Indeed, the difference achieved in frequency and dose was greater than the difference in timing of first mobilisation (median 18 h *vs* 22 h after stroke onset). The trial was well designed and executed, with only six patients lost to follow-up, and external validity seems likely to be good. Participating sites were located in both metropolitan and regional settings, and ranged in size from 33 to 1200 stroke admissions per year. Although the trial took 8 years to recruit patients from 56 acute stroke units, the proportion of eligible patients recruited was higher than in many acute stroke trials,[3] and patient refusals (n=446) were remarkably low. The 3 month mortality rate of only 8% was less than half of that reported in previous acute stroke trials,[4] perhaps because relatively minor strokes were eligible.

The investigators hypothesised that more intensive, early out-of-bed activity would improve functional outcome at 3 months, reduce immobility-related complications, and accelerate walking recovery, with no increase in neurological complications. None of these predictions proved correct. There was no difference in walking recovery between the early mobilisation group and the usual care group, and a good overall functional outcome at 3 months (the primary outcome) was less frequent in the intervention group (adjusted odds ratio [OR] 0·73, 95% CI 0·59–0·90). The unadjusted result for the primary outcome was less convincingly adverse (OR 0·85, 95% CI 0·72–1·00), but the adjustment for age and stroke severity was robust to different analysis methods.

The absence of a difference between the groups in immobility-related complications might partly be due to improvements in stroke-unit practice in the past few years and a move away from prolonged bed rest, such that only 7% of patients in the usual care group stayed in bed for more than 48 h after stroke onset. However, the adverse effect of the intervention on the primary outcome seems to have been driven at least partly by a non-significant increase in neurological deterioration in the intervention group as compared with the usual care group. The non-significant increase in mortality in the intervention group was driven mainly by progression or recurrence (42 such deaths in the intervention group *vs* 26 deaths in the usual care group). The overall increase in mortality in the intervention group was non-significant, and remains so when combined with the few data (15 deaths in 81 patients with early mobilisation *vs* six deaths in 78 patients with usual care) from three small previous trials (fixed-effects OR 1·35, 95% CI 0·99–1·83).[5] Nevertheless, it seems reasonable to conclude that a beneficial effect on mortality is unlikely.

In view of the clinical, causal, and physiological heterogeneity of acute stroke, subgroup–treatment effect interactions might well be expected, and many clinicians had a-priori concern about starting mobilisation early in patients with intracerebral haemorrhage.[6] Therefore, that both the primary outcome (adjusted OR 0·48, 95% CI 0·25–0·92) and 3 month mortality (0·31, 0·11–0·88) were significantly better in the usual care group than the early mobilisation group in patients with intracerebral haemorrhage is noteworthy. The investigators are cautious in their interpretation of this finding on the basis that they did not stratify for stroke subtype at randomisation and did not prespecify any expected subgroup effects themselves, and because no subgroup–treatment effect interaction was statistically significant. However, significance is a poor measure of the validity of subgroup effects,[7] partly because most trials are substantially underpowered to detect them (AVERT recruited only 258 patients with intracerebral haemorrhage). Further analyses of frequency and dose of intervention received in relation to apparent harms could be informative, but updated clinical guidelines should not overestimate the statistical obstacles to interpretation of what seems to be potentially substantial harm in patients with intracerebral haemorrhage, particularly in view of the a-priori clinical concern and evidence that excessive variability in blood pressure, which might be exacerbated by early and intensive mobilisation, is associated with a poor outcome in acute intracerebral haemorrhage.[8] There also seems to be little to lose by a cautious approach to early mobilisation in this group.

AVERT is a milestone in stroke research in that it has shown that large, international, high-quality trials of complex interventions in stroke care, led by physiotherapists and nurses, are possible. The trial contributes several other important lessons. First, it reminds us that high-quality randomised controlled trials of acute stroke so often confound expectations—the overall balance of benefits and harms of any intervention are almost impossible to predict reliably from first principles. Second, it shows

the effect that simple interventions can have on outcome in this physiologically complex and unstable disorder. Findings from the ongoing HeadPoST trial (ClinicalTrials.gov, NCT02162017), comparing the effectiveness of the lying flat (0°) head position with the sitting up (≥30°) head position in the first 24 h of admission to hospital with acute stroke, are likely to be similarly important in this regard. Finally, the low rate of patients refusing to participate in AVERT shows that patients also see the importance of simple, pragmatic research questions. Ironically, the main barriers to more such research are those put up by agencies intended to represent the public interest: the trial regulators with their unnecessarily complex bureaucratic framework for trial performance, which often results in trial prevention, and the medical research funding agencies that in many countries have little interest in the needs of patients and clinicians for answers to pragmatic questions about making the best use of existing interventions in routine clinical practice.[9] Thankfully, those agencies in Australia and the UK that funded AVERT took a different view.

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Bladder catheterisation after female genital fistula repair

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See **Articles** page 56

In *The Lancet*, Mark Barone and colleagues[1] report the results of their study aimed at establishing whether 7 day bladder catheterisation is non-inferior to 14 day catheterisation in terms of fistula breakdown after repair, in women with simple genital fistulas. The traditional 14 day duration of catheterisation after fistula repair has been challenged over the years, although this duration has been widely used in practice.[2–4] A survey of 40 fistula surgeons by Arrowsmith and colleagues[5] reported variability of postoperative catheter drainage strategies ranging from 5 to 42 days.

Barone and colleagues carried out their randomised, controlled, open-label study in hospitals in eight African countries. With 261 patients in the 7 day group and 263 in the 14 day group in the study, no significant difference in fistula repair breakdown, the trial's primary endpoint, was noted between the 7 day and 14 day bladder catheterisation groups (ten [4%] of 250 patients in the 7 day group had repair breakdown *vs* eight [3%] of 251 in the 14 day group, risk difference 0·8% [95% CI −2·8 to 4·5], falling within the predefined non-inferiority margin of 10%). Additionally, no significant differences were noted in secondary outcomes of repair breakdowns 7 days after catheter removal or thereafter; urinary retention 1, 3, or 7 days

STR/Reuters/Corbis

Women recovering from fistula repair in Goma, Democratic Republic of Congo