protection,[8,9] given the potential of wild polioviruses to circulate in populations immunised with IPV alone (as reported recently in Israel),[10] it is unlikely that this protection would be sufficient to curb the spread of a serotype 2 circulating vaccine-derived poliovirus, especially in settings where poor sanitation and hygiene facilitate faecal–oral transmission.

Several gaps in our understanding of poliovirus immunity remain. Of the infants in this study who had not seroconverted to serotype 2 before receiving mOPV2, seroconversion 1 week after challenge was recorded in 127 (71%) of 179 who had received bOPV alone and 20 (53%) of 38 who had received bOPV alongside one dose of IPV. These infants were believed to have been "primed"—an interpretation shared by other recent trials that have reported a similar phenomenon.[6,7] However, we remain uncertain as to the cause of this priming through homotypic or heterotypic mechanisms, and whether or not primed individuals are protected from paralytic disease. Moreover, given that serum neutralising antibodies might begin to appear within 7 days following primary exposure to OPV,[11] this definition of priming is up for debate.

We are entering a phase of major transition in polio immunisation. Even with the encouraging response to serotype 2 reported in this study after one dose of IPV, poor routine immunisation coverage in high-risk areas and the risk of circulating vaccine-derived poliovirus emergence after tOPV withdrawal mean that serotype 2 poliovirus remains a threat to the polio endgame strategy. High-quality surveillance for cases of poliomyelitis alongside enhanced monitoring of waste water and sewage will be key to identifying the persistence of serotype 2 vaccine viruses after tOPV has been withdrawn. We must also be ready to respond rapidly with mOPV2 should an outbreak occur.

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# Is hospital mortality higher at weekends? If so, why?

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In the past few years, politicians, the media, clinicians, and managers have become increasingly interested in the risks involved in being admitted to hospital at weekends. Although higher neonatal mortality has been reported for babies born at weekends than for those born during the week in the USA,[1] the UK,[2] and Australia[3] since the 1970s, the first investigation of a weekend effect in other areas of hospital care was not reported until 2001. Bell and Redelmeier[4] reported higher mortality rates for weekend admissions than for weekday admissions for 23 of the 100 leading causes of death in Canadian hospitals. Since then, studies from around the world have likewise shown differences in mortality between patients admitted at weekends and those admitted during the week. In England, in 2010, Aylin and colleagues[5] showed that the odds of death for emergency admissions were 10% higher at weekends than during the week and, in 2012, Freemantle and

colleagues[6] reported that mortality for all admissions (emergency and elective) was 11% higher on Saturdays and 16% higher on Sundays than on other days during the week.

Widespread interest in England about the possible dangers of being admitted to hospital at weekends has prompted several studies into why this might be, three of which have been published this week. In *The Lancet,* Cassie Aldridge and colleagues[7] provide initial results from an ambitious cross-sectional study evaluating the effect of a natural experiment offered by the roll-out of 7 day services in acute hospitals in England. With a focus on the effect of medical specialist (consultant) staffing levels, the investigators surveyed more than 15 000 specialists in 115 acute hospital trusts to obtain data for the time they each spent caring for emergency admissions on a Wednesday and on a Sunday. The estimated weekend effect showed a 10% increase in mortality for weekend admissions (odds ratio 1·10 [95% CI 1·08–1·11]). Patients received only half as much specialist attention at weekends as on weekdays (median 21·90 [IQR 15·07–29·00] total specialist hours per ten emergency admissions on Sunday *vs* 42·73 h [33·37–55·36]). However, there was no significant association between intensity of specialist staffing and mortality. In view of the response rate to the staff survey (45%), the limitations of basing adjusted mortality on hospital administrative data (which do not provide any biochemical or physiological indication of how sick patients are on admission), and the fact that the study did not consider availability of other staff (eg, junior doctors, nurses), the implications of these results should be interpreted with caution. Although Aldridge and colleagues' findings challenge one of the most widely held views of the cause of higher weekend mortality, establishing whether increasing specialist staffing levels is a beneficial approach must await their secular analyses over the next few years.

Meanwhile, also in *The Lancet,* Benjamin Bray and colleagues'[8] interest is in the level of compliance with evidence-based clinical guidelines. With a focus on stroke care, the investigators overcome some of the limitations of administrative data by using a specialist clinical database that allows them to adjust mortality for differences in the severity of admissions (using the US National Institutes of Health Stroke Score or level of consciousness) on weekdays and at weekends. Whereas a study of stroke admissions based on administrative data in 2009–10 reported a 26% higher mortality for weekend admissions than for weekday admissions,[9] Bray and colleagues' study finds no difference in 30 day mortality in 2013–14; this difference might reflect an improvement in weekend care or could be due to insufficient casemix adjustment in the earlier study. Instead, the investigators suggest we should be more concerned about patients admitted at night, in whom mortality was 10% higher than in those admitted during the day (adjusted odds ratio 0·90 [95% CI 0·82–0·99]). As for adherence to clinical guidelines, such as door-to-needle time and a timely brain scan, patients admitted at night were less likely to receive eight of 12 recommended interventions, which, they suggest, might contribute to heightened mortality. However, before drawing conclusions about the association between adherence to guidelines and outcomes, Bray and colleagues note that although patients admitted at the weekend were also less likely than weekend admissions to receive good quality care, this was not associated with higher mortality.

Christopher Furlong/Staff

In a third innovative approach to investigating the cause of increased weekend mortality, Meacock and colleagues[10] looked beyond the hospital to see the effect of primary care. To do this, the investigators compared the two routes of emergency admissions: direct referrals (mostly from general practitioners) and patients admitted from accident and emergency departments. Whereas the daily number of admissions via accident

and emergency departments at weekends was similar to that on weekdays, the number of direct admissions was 61% lower. While mortality for admissions via accident and emergency was only 5% higher at weekends, for direct admissions it was 21% higher. Given that, apart from initial treatment in accident and emergency, both sets of patients receive the same inpatient care, this finding provides circumstantial evidence that mortality differences are more likely to be attributable to how sick patients are on admission, rather than the quality of hospital care.

In view of these new, albeit inconsistent, insights into the possible dangers of weekend admissions, what conclusions can be drawn and what further research is needed? First, caution should be taken in estimating the effect on mortality. Previous studies based on routine administrative data did their best to use inventive and sophisticated methods to take casemix difference between weekends and weekdays into account, but had little information about how sick patients were on admission. Studies using specialist clinical databases for specific diseases or clinical departments, which include clinical and physiological data, have found little or no significant difference by day of admission.[8,11] Although more such studies are needed to identify which patients might be at risk of weekend admission, what is really needed is a study in which accurate measures of severity are available on all admissions, so that meaningful comparisons of weekends and weekdays for the whole hospital can be made. The increasingly wide use of electronic national early warning scores provides a means of doing that.[12]

Second, even if higher mortality at weekends is accounted for by patients being sicker than during the week, there is a widely held view plus anecdotal evidence that the quality of care is poorer at weekends. The reason this might not be manifest when investigators consider mortality is because death is not a particularly sensitive measure of quality given that only about 4% are thought to be avoidable.[13] Attention should therefore be turned to other measures, such as health outcomes (morbidity, quality of life), safety (falls, hospital-acquired infections), aspects of patients' experience (delays in diagnosis, not receiving sufficient information), operational efficiency (extended lengths of stay, delayed discharges), and educational quality (training of junior doctors at weekends).

Third, perhaps the wrong determinants of poor outcome are being investigated. Maybe nurse staffing levels or the availability of diagnostic staff should be assessed rather than medical staffing.[14] Or perhaps combinations of different professions. But even that approach might not be sufficient because research on inputs, such as staffing levels, risks missing the processes of care, known to be the key determinants of poor quality care.[15] For example, avoidable deaths in hospital happen when a patient's deterioration remains undetected, when staff fail to communicate well with one another, and when the underlying culture of the organisation does not encourage and reward attitudes and behaviours that enhance quality.[16] The importance of such organisational aspects was recognised in 2013 by National Health Service (NHS) England when they recommended ten national clinical standards for emergency admissions, including factors such as access to diagnostics and timely consultant review.[17]

Despite many claims about the quality of care at weekends and strong beliefs about the reasons for this, we need to remain open to the true extent and nature of any such deficit and to the possible causes. Jumping to policy conclusions without a clear diagnosis of the problem should be avoided because the wrong decision might be detrimental to patient confidence, staff morale, and outcomes. As Bray and colleagues warn, "Because solutions are likely to come at substantial financial and opportunity cost, policy makers, health-care managers, and funders need to ensure that the reasons for temporal variation in quality are properly understood and that resources are targeted appropriately."[8]

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# Multiple myeloma—translation of trial results into reality

In the past decade, treatment of multiple myeloma has progressed greatly as a result of several new active drugs, especially lenalidomide and bortezomib.[1,2] In late 2015, three additional new drugs—elotuzumab, daratumumab, and ixazomib—were approved by the US Food and Drug Administration within the space of 2 weeks.[3–5] Several other drugs are in advanced stages of investigation, including isatuximab (a CD38 monoclonal antibody), marizomib and oprozomib (new proteasome inhibitors), filanesib (a kinesin spindle protein inhibitor), dinaciclib (a cyclin dependent kinase inhibitor), venetoclax (a selective BCL-2 inhibitor), ACY-241 (a selective HDAC6 inhibitor), and LGH-447 (a pan-PIM kinase inhibitor).[6] We are concerned that these therapeutic gains might not become a reality for patients because of the absence of a coherent strategy to tackle the heterogeneity of the disease, paucity of strategic trials, and high cost of treatment. We highlight key issues confronting the field, and propose possible solutions. These problems are likely to be a recurring theme in many other cancers, and therefore are relevant to the oncology community as a whole.

Multiple myeloma represents a heterogeneous collection of several different cytogenetically distinct plasma cell malignancies.[7] These entities differ from each other in disease evolution, mode of presentation, response to therapy, and prognosis.[8] Studies to identify the best treatment regimens and sequence of therapy for each subset of the disease are urgently needed. Because researchers will not have adequate numbers of patients for prospective clinical trials in each category, we need comparative effectiveness studies to compare outcomes with the latest regimens in patients with the most common cytogenetic subtypes. Additionally, studies specifically targeting the optimal treatment of secondary cytogenetic abnormalities that are associated with adverse prognosis, such as del(17)(p), gain(1)(q21), and del(1)(p32), are also needed.[9]

Availability of active agents means that there will be many trials testing combinations of two versus three drugs or in the future three versus four drugs, resulting in numerous possible drug combinations. Many of these trials are essential for regulatory approval so that new drugs become available in a timely way to patients, but unfortunately they seldom inform the best strategy for treatment of the disease. To date, the optimal strategy for front-line therapy of multiple myeloma, the nature and duration of maintenance, or the ideal sequence of therapy at relapse cannot be defined from available clinical trials. Some of these issues are to be expected, owing to the rapid pace of drug discovery, but more can be done to advance