similar type of post-hoc analysis in previous large trials (eg, SERAPHIN[10]). However, Hoeper and colleagues did not explain their rationale for including in their analysis all patients (ie, the modified intention-to-treat population), rather than the primary analysis set of patients who met the more stringent inclusion criteria for pulmonary arterial hypertension. One would assume that the main reason was to increase statistical power, since the overall number of deaths in the study was low. Additionally, in exploratory covariate analysis, the authors found that, surprisingly, a higher cardiac index was associated with increased mortality. This finding is certainly at odds with previous observations that baseline haemodynamics, particularly low cardiac output or index, have consistently predicted poor long-term outcomes. Such finding raises the intriguing possibility that combined vasodilator therapy, by causing perhaps an unsuspected deleterious increase in cardiac index, might confound survival results. Another valid concern is whether the low number of deaths in all three groups (either monotherapy and combined therapy) is a significant limiting factor in the interpretation of this post-hoc analysis.

However, Hoeper and colleagues should be complimented for their thought-provoking analysis and findings, which strongly raise the possibility that a radically different therapeutic approach (ie, upfront combination therapy) might improve the only meaningful endpoint (ie, death) in this disease. Other questions that remain unanswered by the AMBITION trial are what specific drug combination works best, and whether upfront combination therapy or sequential add-on therapy, as dictated by clinical deterioration, is the most appropriate approach. Hopefully, Hoeper and colleagues' work will inspire investigators, industries, and regulatory agencies alike to finally consider death as the most relevant endpoint in this disease, despite the obvious challenge of conducting trials of even longer duration to achieve this important goal.

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A practical tool for primary care antimicrobial stewardship in children

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Respiratory tract infections are the single most important cause of consultations in primary care.[1] Approximately 60% of 0–4 year-olds and 30% of 5–15 year-olds present with an acute respiratory infection at least once a year,[1] positioning the primary care consultation for respiratory tract infection as a high-profile target for antimicrobial stewardship initiatives. However, despite national and international calls for more targeted use,[2] primary care prescription of antibiotics for coughs

and colds increased by 40% in the UK between 1999 and 2011,[3] in part reflecting the uncertainties facing patients, parents, and health-care professionals when managing these common but potentially life-threatening infections.

Safety assessments of no antibiotic prescription initiatives for respiratory tract infections will play an important part in gaining public acceptance and successful uptake in practice.[4] Present evidence remains equivocal, suggesting that insufficiently informed reductions in antibiotic prescription in primary care might increase rates of pneumonia diagnosis,[5] hospital admissions, and even mortality.[6] Yet decreased prescribing rates have also been shown to have little effect on rates of rare complications such as mastoiditis, empyema, meningitis, intracranial abscess, and Lemierre's syndrome.[5] Tools that inform antibiotic use according to individualised patient risk profiles could help to realise the benefits of antibiotic stewardship programmes in primary care while minimising potential risks.

In *The Lancet Respiratory Medicine*, Hay and colleagues[7] report the results of a prognostic cohort study to devise a clinical prediction rule to target antibiotic prescribing in children with respiratory tract infections. The aim was to derive (and validate) a clinical prediction rule to improve targeted antibiotic prescribing in children with respiratory tract infections. The study included 8394 children aged 3 months to 15 years presenting with acute cough and respiratory tract infection to 247 general practices in England. Risk of hospital admission in the month after presentation in primary care was assessed. Exposure variables included demographic characteristics, parent-reported symptoms, and physical examination signs. More than a third (3121) of the children were prescribed an antibiotic on the day of consultation, and 78 (1%) were admitted to hospital with a respiratory tract infection in the following 30 days. Irrespective of antibiotic prescription, seven characteristics were independently associated ($p<0·01$) with hospital admission. This statistical analysis underpinned the creation of a seven-item points-based checklist (one point per item) comprising characteristics easily assessable at the point of care: short illness duration (≤3 days); body temperature; age (<2 years); recession; wheeze; asthma; and vomiting (STARWAVe). Using the STARWAVe mnemonic to help structure point-of-care assessment of children presenting with cough and respiratory tract infection should predict the risk of hospital admission with remarkable accuracy (area under the received operating characteristic curve 0·81, 95%CI 0·76–0·85).


Dr P. Marazzi/Science Photo Library

Because the statistical model used to produce the STARWAVe checklist included children prescribed antibiotics (37% of the total study population), it does not reflect the baseline risk of hospital admission in patients not treated with antibiotics. Children with a diagnosis of asthma, who accounted for nearly 10% (750) of the total population, were also included in the study. The fact that asthma was the strong predictor of hospital admission in the STARWAVe checklist despite its presence in only 10% of the patient population could reflect the magnitude of effect of comorbid obstructive airway disease on hospital admission for respiratory tract infection in this young population. Without a separate analysis, it is difficult to know explicitly how well the tool works in the majority, non-asthmatic subpopulation. Validation of the model was only feasible via statistical methods (bootstrapping) with the full scope of intended validation limited by the lower-than-expected hospital admission rate and a consequent lack of statistical power. External validation is important, because (despite high enrolment rates) the study population did not include 164 children whose parents did not consent to the study; consequently, the small minority of severely ill children might not have been fully represented in the study population (only 204 of whom had a STARWAVe score of 4–7). Yet validation attempts using clinical or research databases will be thwarted if, as seems likely, the full range of STARWAVe variables are not collected routinely. A pragmatic alternative might be a prospective pilot study assessing the within-practice effect of future versus historical outcomes (ideally compared with best practice comparator sites to take account of temporal variations in respiratory tract infection), or a cluster randomised trial.

Notwithstanding the inclusion of patients prescribed an antibiotic and the absence of an independent validation cohort, STARWAVe promises to achieve better targeting of antibiotics in primary care. There

are few efficacious interventions for respiratory tract infection available to primary care clinicians beyond offering reassurance and self-management advice, so the modest benefit offered by antibiotics[8] can persuade general practitioners to prescribe them. STARWAVe offers primary care clinicians an evidence-based practical tool to help guide antibiotic prescription decisions and, through shared decision-making, has the potential to reduce antibiotic prescription based on prognostic uncertainty or on non-medical grounds.[9] Combining this tool with point-of-care C-reactive protein (CRP) testing, or to triage for CRP testing,[10] might help to target antibiotic use further.

If STARWAVe leads to an increase in antibiotic prescription (to 90%) in high-risk children and a parallel halving of prescription to those at low risk of hospital admission, it could achieve a 10% overall reduction in primary care antibiotic prescriptions for respiratory tract infections. Within the wider context, the effect of such outcomes on the global burden of antimicrobial resistance will depend on the extent to which its emergence and spread is truly associated with community prescribing as opposed to antibiotic use in hospitals or agriculture.[11]

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Managing threats to respiratory health in urban slums

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More than half the world's population lives in urban areas, and an estimated 863 million people currently live in urban slums.[1] Although urbanisation is usually coupled with economic development, rural-to-urban migration can result in negative implications for respiratory health. Slum residents who live in informal settlements and who commonly have inadequate access to health services are at a particularly high risk of being affected by the dual burden of infectious and non-communicable respiratory diseases over the course of their lives. These diseases include pneumonia in early life; asthma beginning in childhood; and tuberculosis, COPD, and restrictive lung diseases during adulthood. Threats to respiratory health