

Making asthma exacerbations routine: Infrequent outcomes in common conditions through routine data collection

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The end of the summer vacation and return to school brings pleasure to parents, trepidation to teachers, and an air of apprehensive expectation to medical services: the wheeze season will begin in earnest.¹ The perennial upsurge in use of medical services for acute severe wheeze makes school environments a reasonable and valid target for public health measures to improve disease control.² Gerald et al³ report on a school-based crossover interventional study to change hand hygiene among school pupils. More than 17,000 children were studied in 31 schools, of whom 527 had a physician's diagnosis of asthma and agreed to participate in the trial.

The target appears easy: school = pupil mixing = transmission of viruses = asthma exacerbation. Reducing the transmission of viruses should be possible because it has been achieved in health care, where regular hand washing and hand sanitization has been demonstrated as effective in reduction of virus transmission (http://whqlibdoc.who.int/publications/2009/9789241597906_eng.pdf).⁴ Were similar interventions shown to be as helpful in schools, could the effectiveness be gauged by asthma control? In this study by Gerald et al,³ usual care is non-statistically significantly better than the new intervention. Unfortunately, the authors do not provide a point estimate and CI for the primary outcome, and therefore we cannot discuss the likely magnitude of this effect. All we can say is that this study has failed to show a difference. The hand soap in the bathrooms was increased in both trial arms in year 2. This is probably because the schools asked to keep the hand soap dispensers in year 2 if they were allocated them in year 1. Therefore the intervention could not affect bathroom hand soap in the way that was intended. The effects on availability of other cleaning materials go in the right direction, but we cannot tell whether the children were using the cleaning materials differently when they were in the intervention or the control arm. Does this mean that hand hygiene does not work, or did the untimely arrival of the H1N1 pandemic at the start of season 1 also muddy the waters by making hand hygiene *de rigueur* for children irrespective of assigned cohort? Alternatively, is virus transmission only

part of the problem, with greater influence provided by corroborating triggers at the start of the school year?⁵ After all, virus circulation in September is not at its maximum.

The study used a whole-system approach to test a real-life solution to a real-life problem. The cost-effectiveness of the intervention might have been considered reasonable for its introduction across the school sector had the outcome been favorable. Such studies are incredibly useful in helping inform social policy, providing a coherent and cogent strategy for public health policymakers. A real-life interventional approach to asthma care might best alleviate the health, social, and economic burdens of asthma by targeting all those at potential risk.

However, in whole populations asthma events are generally of low absolute risk. The definition of an "asthma event" might encompass the broad spectrum of asthma symptoms, from a brief bronchodilator-responsive cough or wheeze to acute asthma-related death. In the current study the authors defined an asthma event or "exacerbation" as a constellation of inhaler use (>4 puffs) or peak flow (<75% normal) or respiratory-related school-day loss. As outcomes, these were measurable and sufficiently frequent to provide power, but they could be considered mild and self-resolving, possibly better reflecting chronic disease variability.

Recently, increasing emphasis has been given to studies providing a definition of asthma exacerbation to equate with the use of systemic corticosteroids to prevent deterioration or death.⁶ The National Institutes of Health (NIH)'s 2010 Asthma Exacerbations Workshop provided much-needed detail on defining asthma exacerbations.⁷ Common themes across all age ranges were the use of oral corticosteroids and asthma-related admission to the hospital or asthma-related emergency department visit (together with asthma-related intensive care unit admission or death for prospective clinical trials). The NIH definition has provided consensus on a medical perspective of an asthma exacerbation for use as a clinical trial outcome. Although not yet appropriately gauged, the definition is most likely consistent with the view of patients and parents of children with asthma: apprehension of such events and use of oral steroids are predominant in discussions around clinical management. There is also a socioeconomic validity to the NIH definition; patients with asthma who have the most frequent exacerbations (consistent with NIH criteria) not only have greater instability but also have significantly greater costs for associated illnesses and, counter to some belief, have more regular uptake of asthma medicines when compared with those with similar asthma severity who do not have exacerbations.⁸

Gerald et al³ did not report emergency department visits, hospital admissions, or use of oral corticosteroids, presumably because such events were considered too infrequent to be meaningful in this population of 17,000 containing 1,580 children reported to have asthma (including the 527 physician-diagnosed cases recruited to be studied). Therefore the conundrum is how to study infrequent events in whole populations.

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Asthma exacerbations consistent with the NIH definition are infrequent in whole populations: in a survey of US households, 3% of all adults had an asthma exacerbation in the previous year.⁹ Were a trial to be devised to reduce the population's exacerbation frequency to 2%, approximately 12,000 participants would be required. The requirement for such a large number of participants places significant limitations on the practical evaluation of interventions to reduce acute asthma events in real-world clinical trial designs.

Restricting study populations to persons with a diagnosis of asthma (regardless of severity) might increase the relative risk of an event, but even in these scenarios the bulk of patients with mild controlled disease retain the relatively low absolute risk of an acute NIH-defined asthma event.⁵ In those with mild persistent asthma, the risk of a severe asthma exacerbation has been reported to be as low as only a 1 in 56 chance (0.018 exacerbations per person per year) in those receiving no regular treatment and only a 1 in 100 chance (0.01 exacerbations per person per year) for those taking regular low-dose inhaled corticosteroids.¹⁰

Further honing down study populations to those at most risk of an asthma exacerbation can most practically capture those most suitable for intervention. Asthma exacerbations in adults are twice as likely in those with poor control,⁹ and children are twice as likely to have an exacerbation requiring oral prednisolone if they have previously had oral steroids for an asthma exacerbation.¹ However, these highly defined populations are captured at a cost; the characteristics of those with frequent repeat episodes might not be those of the asthma population with infrequent events. In addition, the ability of health systems to precisely identify subjects with such frequent exacerbations on a progressive basis is often imperfect in practice.

In the majority of persons with a recent previous episode of severe wheeze, the risk to a subject of at least 1 subsequent NIH-defined acute asthma exacerbation in the next 12 months is in the region of 70%. This event rate has been reported in preschoolers with wheeze (0.78 events per person per year),¹¹ school-aged children with mild-to-moderate asthma receiving treatment (0.70 per person per year),¹² and adults (0.73 per person per year).¹³

In studies proposing intervention in populations preidentified as at greatest risk of an asthma exacerbation, reducing the NIH combined outcomes by 20% to 50% would require only 300 patients (assuming 90% power and 10% missing data), but this would increase to 1100 participants if the benefit was only a 10% reduction and 4200 for a 5% reduction. These are attainable sample sizes: asthma is not particularly rare, and even the largest of these sizes would be achievable if a trial was kept very simple. However, when applied to whole populations rather than those at most risk, the numbers required become unwieldy for most standard interventional trials; a reduction in exacerbation frequency from 70% to 60% would need 70,000 persons, and an intervention improving the frequency by 5% (70% to 65%) would require 285,000 persons.

Is it possible to have our cake and eat it? Will we continue to need separate outcomes for asthma events depending on whether interventions are tested on whole populations or defined asthma populations? Or can we create functional trial designs that can determine the outcome of the infrequent few when assessing the majority across the disease spectrum? If an intervention were focused at a population rather than at subjects with asthma, the sample size would need to be much larger, but routinely collected data could be used to make such a study feasible and practical. Electronic health records are increasingly adopted in health

systems,¹⁴ facilitating large-scale interventional programs to look at important outcomes in using routinely collected data.¹⁵ Although currently used for pragmatic and quasirandomized controlled trials,¹⁶ their potential lies in the styles of intervention applied by Gerald et al³ or larger public health interventions and also, of course, for the assessment of licensed medicines after registration. Universal unique patient identifiers and standardization of routinely collected data are already enabling some researchers to begin to interrogate health systems for components of the NIH-defined asthma exacerbations,¹⁷ and complete acquisition is soon to be reported (personal communication, Professor Graham Devereux, University of Aberdeen, United Kingdom, using Information Services Division Scottish health database). This ability is disappointingly limited because such national systems are, as yet, in their infancy. Therein lies the opportunity: clinicians should suggest, at the local and governmental levels, for NIH asthma exacerbation criteria events to be embedded in routinely collected health care data. We will need this capability to research future potential population health improvements in this most common respiratory condition.

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