In summary, Owens and coworkers (5) have shown that *in utero* smoke exposure is associated with PFT deficits later in life. They argue that *in utero* smoke affects lung size, and that this effect is modulated by antioxidant genotype. Although more studies are needed, this article confirms the value of primary prevention to mitigate the adverse effects of *in utero* smoke exposure on the sensitive fetal lung. ■

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Fail-Fast in Respiratory Syncytial Virus Vaccine Development

Despite of progress made for the past decades in the field of respiratory syncytial virus (RSV), we are still lacking a safe and effective RSV vaccine. In the absence of a correlate of protection to RSV, vaccine developers are working in the dark, and therefore often find out that their product is insufficiently effective (1). For example, Novavax developed a nanoparticle-based RSV vaccine for older adults and went through a large phase 2b trial, only to find out it was not effective in a large phase 3 trial (2). Novavax got back on its feet and is currently unblinding their next phase 3 trial, now in pregnant women (3). To accelerate RSV vaccine development, developers adopted the fail-fast approach.

Fail-fast systems were designed to immediate report failure to stop product development, rather than continue developing a product that likely will never be good enough. The fail-fast approach has been adopted by the pharmaceutical industry and became the mantra of many start-up companies not only to prevent wasting efforts, but also to create a healthy society in which entrepreneurs can fail, learn and improve (4). However, the fail-fast strategy has its own challenges, which are illustrated in this issue of the *Journal* by Ascough and colleagues (pp. 481–492) (5). In their article, they describe the results of a phase 1 study of a novel needle-free RSV vaccine: SynGEM. The vaccine is based on a stable prefusion F antigen of the virus and uses a bacterial-like particle as an

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immune-enhancing carrier. The vaccine had already been shown to protect against infection in mice and cotton rats on RSV challenge (6). Now, healthy adult volunteers were vaccinated using a prime-boost approach. The authors used conventional methods to measure induced antibodies, including nasal IgA levels, serum neutralization, and palivizumab competing assays. The vaccine was safe and induced a twofold rise in specific antibodies, including when participants were seropositive at the start of the trial. RSV-specific mucosal IgA concentrations against RSV were variable, with the strongest increase in individuals with low preexistent levels of mucosal antibodies. Furthermore, the vaccine induced an increase in concentration of circulating RSV-specific B cells determined by ELISpot. However, despite the use of a subunit vaccine based on the stabilized pre-F protein, there was no induction of neutralizing antibodies. Unfortunately, these results were not convincing enough to grant funding for a human challenge trial.

This study is important and well performed, given the challenges of doing this with limited resources of an early-phase clinical trial. The study sets an example that collaboration between a relatively small biotech company, such as Mucosis, and the highly experienced RSV research team at Imperial College has the potential of developing vaccines with worldwide impact. Unfortunately, the study did not reach the endpoint threshold, and SynGEM was withheld from proceeding to next-phase trials. Was this a rushed decision?

To answer this question, we should think about RSV vaccine development in general. The development of an RSV vaccine is hampered by several problems. First, there is no optimal animal model. Mice can be infected with human RSV, but they lack many of the clinical characteristics of RSV bronchiolitis in children. Cotton rats are often used to develop therapeutics but do not reliably predict efficacy of antivirals or vaccines against RSV. In addition, the formalin-inactivated RSV vaccine, which caused vaccine-augmented disease, led to great caution taking an RSV vaccine into seronegative infants (7). Most important, we lack serological markers of protection to RSV. There is evidence that suggests mucosal IgA is protective against RSV, and neutralizing antibodies against RSV-pre-F show high neutralizing activity (8, 9). Still, this does not guarantee that the vaccine protects against RSV infection. Until we have established correlates of protection to RSV, we are left with trial-and-error approaches, such as those used for SynGEM in this article. Considering the risk that vaccines might still fail during late-stage clinical trials, manufacturers are vexed on how to move forward with clinical development. This uncertainty may well have contributed to the premature ending of potentially safe and effective RSV vaccines, which would be detrimental to the development of a working vaccine. A possible way to negate these adverse effects, and a more secure option in the fail-fast approach, would be to use the human challenge model.

In the case of SynGEM, the decision to discontinue vaccine development resulted in discontinuation of funding and the bankruptcy of Mucosis. Could this public–private partnership have used a human challenge study to add value to the decision whether or not to continue the clinical development of SynGEM? The human challenge model has limitations, including the use of a single viral strain, absence of the target population (infants), and relatively mild disease severity. Nevertheless, human challenge studies can quickly provide proof of concept of efficacy of novel RSV therapeutics, as is acknowledged by the World Health Organization and regulators (10–13). The authors are part of the publicly funded prestigious HIC-Vac network, which is hosted at Imperial College, London, which can perform a human challenge with SynGEM in healthy volunteers. As Virtuvax has now taken over Mucosis' vaccine technology, this may still be a viable option to get the answer to the critical question whether or not immunity by SynGEM could be protective.

In conclusion, the authors have provided compelling evidence that bacterial-like particle–based vaccines may have a future, in particular for RSV infection. However, the conclusions of this study leave us with a dilemma. On the one hand, the vaccine may deserve a second chance in a human challenge study to define clinical protection. On the other, after the fail-fast culture, we should be bold enough to terminate a program without hesitation, as this allows us to move on and develop an even better program to fight one of the most deadly diseases during infancy. ■

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Sleep Apnea Heterogeneity, Phenotypes, and Cardiovascular Risk
Implications for Trial Design and Precision Sleep Medicine

Obstructive sleep apnea (OSA) affects 25 million adults in the United States and is linked to major causes of morbidity and mortality, including coronary heart disease, heart failure (HF), stroke, and atrial fibrillation (1–4). Importantly, patients with sleep apnea are heterogeneous with respect to symptoms, physiologic traits linked to disease pathogenesis, and the polysomnographic expression of this disorder (e.g., severity of hypoxemia and sleep architectural changes).

Despite this variability, clinical sleep medicine focuses on "cutoffs" or threshold values of a single metric (i.e., the apnea–hypopnea index [AHI]) for diagnosis and severity grading of OSA. However, these threshold values are not the best predictor of OSA-related morbidity, and the field is now questioning the use of the AHI as the primary diagnostic or prognostic criterion for patients with sleep-disordered breathing. Indeed, various health outcomes may be related to sleep apnea through distinct pathophysiologic pathways that differentially reflect responses to hypoxemia, arousal (5), and sleep state (6). Should we be using one, two, or more of these sleep-associated measures to follow patients with sleep apnea?

Recently, a number of studies have begun to leverage the inherent heterogeneity in OSA and shed light on this question by using methods that can be broadly classified as either supervised or unsupervised analytic approaches (7). Supervised approaches involve the evaluation of prespecified hypotheses and often involve traditional regression modeling methods applied to single or few features. Recent excellent examples of this approach include observations that REM sleep apnea (6) and hypoxic burden (8) significantly increase cardiovascular risk in patients with sleep apnea. In contrast, unsupervised methods focus on discovering emergent patterns within the data, often use cluster or neural network analyses, and examine many features to generate hypotheses. Applying this approach to various domains of polysomnographic variables, Zinchuk and colleagues observed that there were multiple clusters of patients within traditional AHI severity cutoff groups, and that some were significantly associated with adverse cardiovascular outcomes (9). Importantly, they found a variable responsiveness to continuous positive airway pressure (CPAP) therapy in attenuating cardiovascular risk among these clusters.

Together, these data may in part explain the negative findings of recent randomized controlled trials focused on cardiovascular outcomes (10, 11). In addition, these trials tended to focus on patients who were not excessively sleepy, given the ethical challenges posed by randomization of such individuals to receive no specific treatment (e.g., with respect to motor vehicle accident risk). Lack of sleepiness may have also contributed to lower than expected CPAP adherence (12), another plausible contributor to the null results of these trials.

It is in this context that Mazzotti and colleagues (pp. 493–506) present their paper entitled "Symptom Subtypes of Obstructive Sleep Apnea Predict Incidence of Cardiovascular Outcomes" in this issue of the *Journal* (13). In this study, the authors aimed to characterize OSA symptom subtypes and assess their association with prevalent and incident cardiovascular disease (CVD) in the successful community-based Sleep Heart Health Study. Using latent class analysis (an unsupervised approach), they observed four subtypes of symptoms: disturbed sleep (12.2%), minimally symptomatic (32.6%), excessively sleepy (16.7%), and moderately sleepy (38.5%). Similar symptom subtypes have been previously observed in other population-based (14) and clinical (15) samples, reinforcing their validity. In adjusted models, the "excessively sleepy" subtype was associated with a more than threefold increased risk of prevalent HF compared with each of the other subtypes. Symptom subtype was also associated with incident CVD ($P < 0.001$), coronary heart disease ($P = 0.015$), and HF ($P = 0.018$), with "excessively sleepy" again demonstrating increased risk (hazard ratios of 1.7–2.4) compared with other subtypes.

This study highlights the importance of considering symptom subtypes when designing trials to assess the cardiovascular benefits of CPAP treatment. For example, the RICCADSA (Continuous Positive Airway Pressure [CPAP] Treatment in Coronary Artery Disease and Sleep Apnea) study (11), a randomized trial in individuals with severe OSA who were not excessively sleepy, found no cardiovascular benefit of CPAP in intention to treat analyses. Similarly, the much larger SAVE (Continuous Positive Airway Pressure Treatment of Obstructive Sleep Apnea to Prevent

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