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Smoking and e-cigarette use: key variables in testing IgA-oriented intranasal vaccines

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Vaccines are an essential component in the fight against highly virulent respiratory pathogens such as influenza virus, *Bordetella pertussis,* and SARS-CoV-2. Although most existing vaccines for respiratory pathogens are injectable, development of efficacious intranasal vaccine formulations is a clear goal for the immunological community, especially as a result of the SARS-CoV-2 pandemic.[1] Beyond the logistical benefits of needle-free vaccination,[2] intranasal vaccines aim to induce mucosal immune responses in addition to systemic immunity, providing an additional layer of protection at the vulnerable respiratory interface.[1]

One important component of mucosal immunity is the induction of secretory IgA antibodies, which can help to neutralise inhaled microbes to preclude pathogen acquisition and dissemination, particularly in the upper airways. Induction of secretory IgA is a major impetus in the development of mucosal immunisation strategies.[1,2] Ultimately, although injectable vaccines are able to reduce the burden of respiratory disease, intranasal vaccines have the potential advantage of limiting disease transmission by better defending the airway mucosa, a frequent site of initial infection. Vaccines that protect against acquisition and transmission, as well as severe disease following infection, have the potential to further reduce the health-care burden associated with respiratory pathogens.

Given that intranasal vaccines target the upper airways, it is of interest whether inhaled irritants such as cigarette smoke and e-cigarette aerosols (which both affect numerous immune functions[3,4]) impair mucosal aspects of intranasal vaccine efficacy. Some studies have shown decreased total salivary IgA levels in smokers,[5] whereas others have shown that smoking increases oral IgA.[6] Although little is known about the impact of smoking on antigen-specific IgA induction following respiratory infection in humans, the nasal secretions of smokers have been shown to contain lower levels of lipopolysaccharide-specific IgA than those of non-smokers,[7] indicating that some local deficit might exist. By comparison, serum haemagglutination-inhibiting antibody titres did not differ between smokers and non-smokers following intranasal live-attenuated influenza virus vaccine immunisation,[8] suggesting that systemic adaptive responses to mucosal vaccination are not broadly impaired. However, this study did not assess IgA induction in the upper airways.

Recently, our research groups[9,10] showed that cigarette smoke and e-cigarette exposure can interfere with the induction of antigen-specific IgA immunity in the upper airways. In humans, Rebuli and colleagues[9] showed that the induction of influenza-specific IgA was diminished by about 40% in the nasal lavage fluid of smokers and e-cigarette users at day 8 following live-attenuated influenza virus immunisation relative to never-smokers. In mice, McGrath and colleagues[10] showed that intranasal immunisation with lipopolysaccharide and ovalbumin during concurrent cigarette smoke exposure resulted in

diminished nasal ovalbumin-specific IgA responses for at least 1 month relative to room air-exposed controls. This decreased response was associated with a reduced accumulation of ovalbumin-specific IgA antibody-secreting cells in the nasal mucosa, and reduced induction of these cells in the nasal-associated lymphoid tissue, cervical lymph nodes, and spleen.[9] In aggregate, these data support the idea that both tobacco smoke and e-cigarette aerosols, which vary substantially in composition, can compromise antigen-specific IgA induction in the upper airways.

The financial cost of developing one preclinical epidemic pathogen-associated vaccine candidate up to the completion of phase 2a clinical trials is estimated to be US$14–159 million.[11] However, after considering failed alternative candidates at each stage, this range increases nearly tenfold to $137 million–$1·1 billion.[11] This cost illustrates the importance of mitigating failure risk within the vaccine development pipeline. Variables that can interfere with critical readouts need to be categorically accounted for during clinical testing. In this regard, the studies discussed previously[7,9,10] provide reasonable evidence that cigarette or e-cigarette use can detrimentally impact IgA-based immunity in the upper airways. At a minimum, their use could introduce variability and skew the interpretation of IgA-related data, and at worst, promote discontinuation of intranasal vaccine candidate trials for which IgA induction is a primary outcome. To reduce these risks, and ensure candidate efficacy in exposed populations, we recommend that cigarette and e-cigarette exposure be consistently considered in all phases of clinical testing for IgA-oriented intranasal vaccines. We propose two possible approaches. First, clinical trials with sufficient cohort size focusing on IgA-oriented intranasal vaccines should collect data regarding smoking, e-cigarette use, and second-hand exposure to perform subgroup analyses for effect modification by these variables. Second, phase 1 trials (or any phase with restricted cohort size) focusing on IgA-oriented intranasal vaccines should, given their typically limited cohort size, consider excluding tobacco smokers, e-cigarette users, ex-users with substantial use history, and individuals with high second-hand exposures to these products.

To determine historical omission of these variables, we searched ClinicalTrials.gov for trials of intranasal vaccines that had an explicit or inferred focus on secretory IgA induction and assessed whether they considered smoking and e-cigarette use within exclusion or inclusion criteria. Among the 42 registered trials for respiratory pathogens conducted to Oct 20, 2021, with IgA or mucosal antibodies listed as an outcome measure under study details or tabular view, only 16 (38%) considered smoking status among the participants (age ≥15 years). Within the studies that did consider these variables, exclusion criteria varied: nine (56%) of 16 omitted current smokers (often unclearly defined), eight (50%) omitted anyone with a smoking history (with variable thresholds), and six (38%) merely required cessation of smoking during the study period. Furthermore, only five (12%) of the 42 studies had criteria that omitted e-cigarette users, and none considered second-hand exposure.

Overall, although we recommend the exclusion of smokers and e-cigarette users in small clinical trials to limit the effect of these confounding variables, these subpopulations should instead be recruited (at any phase of testing) in trials that have sufficient cohort size and power to test outcomes in these individuals. Given that effects dependent on dose level (eg, smoking pack-years) are often observed, studies would ideally collect both qualitative and quantitative measurements including number of cigarettes smoked or e-cigarette puffs per day, type of e-cigarettes used, estimated duration of use, time since cessation in ex-users, levels of second-hand exposure, and serum and urine cotinine levels if available. The application of the aforementioned recommendations has the potential to improve the efficiency of clinical trials for IgA-oriented intranasal vaccines, while providing valuable information about candidate efficacy in smokers, e-cigarette users, and second-hand smoke-exposed populations.

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Transcriptomics in the intensive care unit

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Disruption of body homeostatic mechanisms that necessitate initiation of life-support therapy can result from a variety of biological insults. One commonly encountered cause is infection. Severe infections resulting in damage to distant body organs are a major cause of death and morbidity worldwide. This combination, known as sepsis, arises from a variety of pathogens and manifests in various ways.[1] Sepsis is a leading cause of death, accounting for an estimated 20% of all deaths globally in 2017.[2] Data collected for adult hospital admissions as a result of severe sepsis in seven high-income countries showed that of 19·4 million admitted patients, 5·3 million died, amounting to mortality above 25%.[3] Although early recognition and initiation of treatment are key to improving outcomes, management of sepsis remains a challenge despite major advances in medical science. Variation in the type of pathogen, size of inoculum, site of infection, the presence or absence of haematogenous spread, damage to one or more organs, and patient comorbidities all combine to form a complex picture. Such complexity brings enormous challenges, not only in researching the syndrome, but also in subsequent development of effective therapies.

There is no gold-standard diagnosis of sepsis. The heterogeneity of patients grouped under the diagnosis

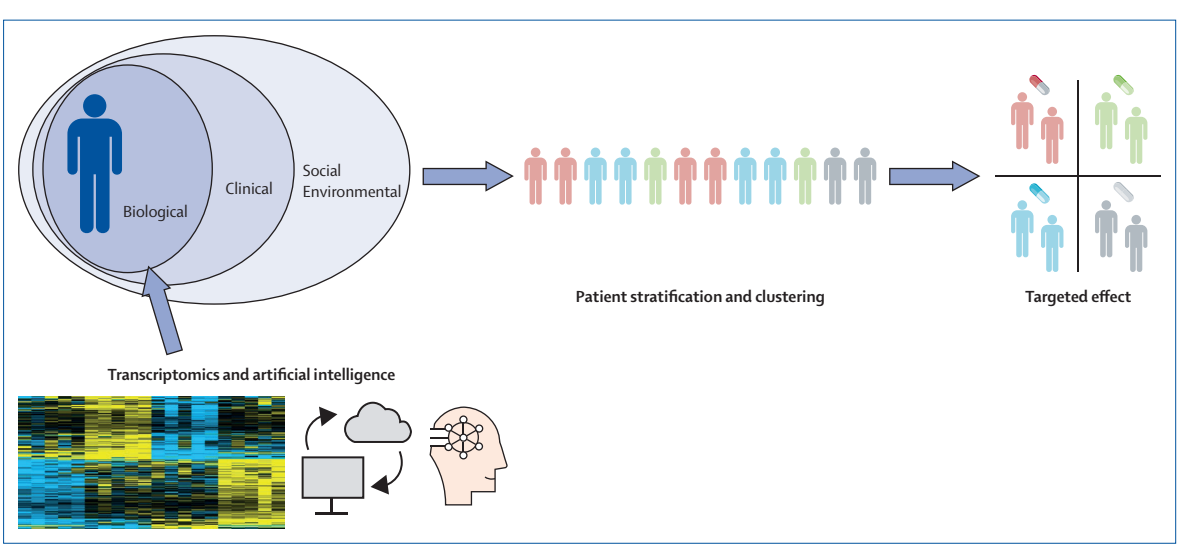

Figure: **Transcriptomic data integration for personalised medicine**