

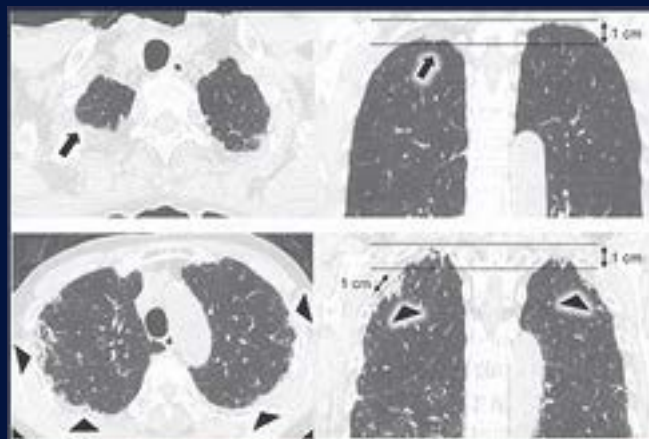
# Thorax

ORIGINALITY, RIGOUR & EXCELLENCE IN RESPIRATORY MEDICINE

com artigos do

ARCHIVES OF  
DISEASE IN  
CHILDHOOD

Edição Portuguesa



Vacina  
disponível na  
época gripal  
2023/24

PARA ADULTOS COM 60 OU MAIS ANOS DE IDADE

# EFLUELDA®

AJUDA A QUEBRAR O CIRCUITO DA GRIPE

4x

MAIS ANTIGÉNIO  
por estirpe vs. vacina  
de dose padrão<sup>1,2</sup>

+24,2%  
(IC 95%; 9,7% - 36,5%)

EFICÁCIA RELATIVA SUPERIOR  
vs. vacina de dose padrão em indivíduos  
com 65 ou mais anos de idade<sup>1,3</sup>

sanofi

**Efluelda®**  
Vacina quadrivalente contra a gripe  
(vírião fragmentado, inativado), 60 mcg HA/estirpe

#### REFERÊNCIAS:

1. DiazGranados CA, et al. (2014). Efficacy of High-Dose versus Standard-Dose influenza vaccine in older adults. New England Journal of Medicine, 371(7): 635-645. doi:10.1056/NEJMoa1315727 2. CDC. Fluzone High-Dose Seasonal Influenza Vaccine. 2022. Disponível em: [https://www.cdc.gov/flu/prevent/qa\\_fluzone.htm](https://www.cdc.gov/flu/prevent/qa_fluzone.htm). Último acesso em Julho 2023. 3. RCM Efluelda® Agosto 2023.

Este medicamento está sujeito a monitorização adicional. Isto irá permitir a rápida identificação de nova informação de segurança. Pede-se aos profissionais de saúde que notifiquem quaisquer suspeitas de reações adversas. Para saber como notificar reações adversas, ver secção 4.8. do RCM completo. **Nome do medicamento:** EFLUELDA, suspensão injetável em seringa pré-cheia. Vacina quadrivalente contra a gripe (vírião fragmentado, inativado), 60 microgramas HA/estirpe. **Composição Qualitativa e Quantitativa:** Vírus da gripe (inativado, fragmentado) das seguintes estirpes\*: A/Victoria/4897/2022 (H1N1) pdm09 - estirpe análoga (A/Victoria/4897/2022, IVR-238) 60 microgramas HA\*\*, A/Darwin/9/2021 (H3N2) estirpe análoga (A/Darwin/9/2021, SAN-010) 60 microgramas HA\*\*, B/Austria/1359417/2021 - estirpe análoga (B/Michigan/01/2021, tipo selvagem) 60 microgramas HA\*\*, B/Phuket/3073/2013 - estirpe análoga (B/Phuket/3073/2013, tipo selvagem) 60 microgramas HA\*\*. Por dose de 0,7 ml, \* propagados em ovos de galinha embrionados \*\* hemaglutinina. Esta vacina está conforme as recomendações da OMS (Hemisfério Norte) e a decisão da UE para a época de 2023/2024. EFLUELDA pode conter vestígios de ovos, como ovalbumina, formaldeído que são utilizados durante o processo de fabrico (ver secção 4.3). Lista completa de excipientes, ver secção 6.1 do RCM Completo. **Forma Farmacéutica:** Suspensão injetável em seringa pré-cheia. Após agitação suave, EFLUELDA é um líquido incolor opalescente. **Indicações terapêuticas:** EFLUELDA está indicado para a prevenção da gripe, como imunização ativa dos adultos com 60 ou mais anos de idade. A utilização de EFLUELDA deve basear-se nas recomendações oficiais sobre a vacinação contra a gripe. **Posologia e modo de administração:** Posologia: Em adultos com 60 ou mais anos: uma dose de 0,7 ml. População pediátrica: A segurança e eficácia de EFLUELDA em crianças com menos de 18 anos de idade não foram estabelecidas. **Modo de administração:** A via de administração preferencial para esta vacina é a via intramuscular embora possa também ser administrada por via subcutânea. O local recomendado para a injeção intramuscular é a região deltoide. A vacina não deve ser injetada na região glútea ou em áreas onde possa existir um tronco nervoso principal. Para instruções acerca da preparação do medicamento antes da administração, ver secção 6.6. do RCM completo. **Contra-indicações:** Hipersensibilidade à substância ativa ou a qualquer um dos excipientes mencionados na secção 6.1 do RCM completo ou a qualquer componente que possa estar presente em quantidades vestigiais, como resíduos de ovo (ovalbumina, proteínas de galinha) e formaldeído. **Efeitos indesejáveis:** a. Resumo do perfil de segurança: A informação sobre reações adversas é baseada em dados provenientes de dois ensaios clínicos com EFLUELDA e na experiência clínica e de pós-comercialização com a vacina trivalente contra a gripe (vírião fragmentado, inativado) de dose elevada (TIV-HD). A segurança de EFLUELDA foi avaliada numa análise conjunta de dois ensaios clínicos (QH000013 e QH000011) em que 2549 adultos de 60 ou mais anos de idade (378 adultos de 60 a 64 anos de idade e 2171 adultos com 65 ou mais anos) receberam EFLUELDA. A reação adversa notificada com mais frequência após a vacinação foi dor no local da injeção relatada por 42,6% dos participantes do estudo, seguida por mialgia (23,8%), dor de cabeça (17,3%) e mal-estar (15,6%). A maioria destas reações ocorreu e resolveu-se dentro de três dias após a vacinação. A intensidade da maioria destas reações foi leve a moderada. No geral, as reações adversas foram geralmente menos frequentes em participantes com 65 ou mais anos do que em participantes com 60 a 64 anos. A reatogenicidade de EFLUELDA foi ligeiramente aumentada em comparação com a vacina de dose padrão, mas não foi observada nenhuma grande diferença na intensidade. A segurança de EFLUELDA (QIV-HD) foi avaliada num estudo descritivo (QH000028) no qual os indivíduos receberam QIV-HD juntamente com uma dose de reforço experimental de 100 microgramas da vacina de mRNA COVID-19 (com nucleósido modificado) (n=100), indivíduos que apenas receberam QIV-HD ou uma dose de reforço experimental de 100 microgramas da vacina mRNA COVID-19 (com nucleósido modificado) (n=104). A frequência e gravidade das reações adversas locais e sistémicas foram semelhantes em indivíduos que foram coadministrados com QIV-HD e vacina mRNA COVID-19 e indivíduos administrados apenas com uma dose de reforço da vacina mRNA COVID-19. b. Resumo das reações adversas em forma tabelar: Os dados abaixo resumem a frequência de reações adversas que foram notificadas no seguimento da vacinação com EFLUELDA e as reações adversas notificadas durante o desenvolvimento clínico e a experiência pós-comercialização com a vacina TIV-HD (marcado com \*). As reações adversas encontram-se listadas sob títulos de frequência utilizando a seguinte convenção: Muito frequentes (≥1/10); Frequentes (≥1/100 a <1/10); Pouco frequentes (≥1/1.000 a <1/100); Raros (≥1/10.000 a <1/1.000); Muito raros (<1/10.000); Desconhecido (não pode ser calculado a partir dos dados disponíveis). **REAÇÕES ADVERSAS - FREQUÊNCIA:** **Perturbações gerais e alterações no local de administração:** Dor no local de injeção, eritema no local da injeção, mal-estar - Muito frequentes; Tumorção no local de injeção, induração no local de injeção, contusão no local de injeção, febre (≥37,5°C), arrepios - Frequentes; Prurido no local de injeção, fadiga - Pouco frequentes; Astenia - Raros; Dor torácica - Desconhecido\*. **Afeções musculoesqueléticas e dos tecidos conjuntivos:** Mialgia - Muito frequentes; Fraqueza muscular - Pouco frequentes; Artralgia, dor nas extremidades - Raros. **Doenças do sistema nervoso:** Cefaleia - Muito frequentes; Letargia - Pouco frequentes; Tontura, parestesia - Raros; Síndrome de Guillain-Barré (SGB), convulsões, convulsões febris, mielite (incluindo encefalomielite e mielite transversa), paralisia facial (paralisia de Bell), neurite ótica/neuropatia, neurite braquial, síncope (logo após a vacinação) - Desconhecido\*. **Doenças do sangue e do sistema linfático:** Trombocitopenia, linfadenopatia - Desconhecido\*. **Doenças respiratórias, torácicas e do mediastino:** Tosse, dor orofaríngea - Pouco frequentes; Rinorria - Raros; Dispneia, sibilos, aperto da garganta - Desconhecido\*. **Doenças gastrointestinais:** Náusea, vômitos, dispepsia, diarreia - Pouco frequentes. **Doenças do sistema imunitário:** Prurido, urticária, suores noturnos, rash - Raros; Anafilaxia, outras reações alérgicas/hipersensibilidade (incluindo angioedema) - Desconhecido\*. **Vasculopatias:** Rubor - Raros; Vasculite, vasodilatação - Desconhecido\*. **Afeções do ouvido e do labirinto:** Vertigens - Raros. **Afeções oculares:** Hiperemia ocular - Raros. **Dispepsia, letargia e fraqueza muscular** foram observadas com TIV-HD no ensaio QH000013. **Notificação de suspeitas de reações adversas:** A notificação de suspeitas de reações adversas após a autorização do medicamento é importante, uma vez que permite uma monitorização contínua da relação benefício-risco do medicamento. Pede-se aos profissionais de saúde que notifiquem quaisquer suspeitas de reações adversas diretamente ao INFARMED, I.P.: Sítio da internet: <http://www.infarmed.pt/web/infarmed/submissao> (preferencialmente) ou através dos seguintes contactos: Direção de Gestão do Risco de Medicamentos Parque da Saúde de Lisboa, Av. Brasil 53 1749-004 Lisboa Tel: +351 21 798 73 73 Linha do Medicamento: 800222444 (gratuita) E-mail: [farmacovigilancia@infarmed.pt](mailto:farmacovigilancia@infarmed.pt) Data da revisão do texto: Agosto 2023 Medicamento Sujeito a Receita Médica. Não comparticipado. Para mais informações contactar o Representante Local do Titular da Autorização de Introdução no Mercado.



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Estamos praticamente a terminar o ano de 2023, e estamos de volta com mais um número da edição em língua portuguesa de artigos selecionados das revistas Thorax e Archives of Disease in Childhood.

As notícias de que fizemos eco em anterior editorial do presente ano sobre as dificuldades do Serviço Nacional de Saúde Português no que respeita ao recrutamento e retenção de profissionais de saúde, ao subfinanciamento, e às questões organizacionais e estruturais têm-se agravado nos últimos meses do ano. A atual situação política de período pré-eleitoral e de alteração da equipa governamental não permitem a estabilidade necessária para lidar de forma eficiente com os atuais problemas do SNS.

Em virtude da dissolução da Assembleia da República, ficou também suspensa a aprovação da legislação sobre uma maior regulação e controlo do uso de produtos do tabaco, tão importante para a promoção da saúde e prevenção de doença respiratória, oncológica e cardiovascular. Teremos de aguardar pela formação do novo governo para poder retomar a iniciativa legislativa com a esperança que venha finalmente a ser aprovada.

Neste número da Revista, chamamos a sua atenção para alguns artigos.

O primeiro é o artigo “Eficácia da distribuição de medicamentos preventivos da asma para prevenir readmissões por asma na infância: um estudo de coorte interligado com vários locais” e teve como objetivos descrever a distribuição de medicamentos preventivos de asma na alta hospitalar, estimar o seu efeito nas readmissões e estimar o efeito da distribuição comunitária desses medicamentos nas readmissões de crianças. O estudo conclui que se verificou uma baixa taxa de prescrição e dispensa de medicamentos preventivos de asma na alta hospitalar e não foi encontrado qualquer efeito protetor para o seu impacto nas readmissões. No entanto, verificou-se um efeito protetor nas readmissões para a dispensa comunitária de medicamentos preventivos de asma. O segundo artigo intitula-se “Resposta broncodilatadora por técnica de interrupção para orientar o tratamento da pieira pré-escolar”. Os autores desenvolveram um estudo clínico não aleatorizado com intervenção tendo examinaram as relações entre as características clínicas e a função pulmonar antes e depois do tratamento com corticosteroides inalados em crianças em idade pré-escolar com pieira e, especificamente, se a medição da resposta ao broncodilatador poderia prever o benefício do tratamento com corticosteroides inalados. A conclusão foi que a resposta ao broncodilatador por técnica de interrupção pode ser útil para selecionar as crianças em idade pré-escolar com pieira que poderão beneficiar de tratamento com corticosteroides inalados.

Sugere-se ainda a leitura do artigo “Melhor prescrição de antimicrobianos pediátricos com um aplicativo para smartphone: um estudo intervenção antes e depois”, cujo objetivo era melhorar a adesão às diretrizes clínicas locais existentes tanto para infeções em adultos como pediátricas. Após a introdução de uma aplicação de apoio à prescrição, verificou-se uma melhoria significativa e sustentada na adesão às diretrizes antimicrobianas pediátricas.

Os restantes artigos merecem também uma leitura atenta. Esperamos que a atual seleção seja do agrado dos leitores.

Desejamos a todos umas boas festas e um bom ano de 2024 e regressaremos em março com novas escolhas.

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## ARTIGO ORIGINAL

# Eficácia da distribuição de medicamentos preventivos da asma para prevenir readmissões por asma na infância: um estudo de coorte interligado com vários locais

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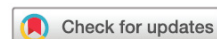
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## RESUMO

**Objetivos** — Para (1) descrever a distribuição de medicamentos preventivos de asma na alta hospitalar e estimar o seu efeito nas readmissões hospitalares e (2) estimar o efeito da distribuição comunitária de medicamentos preventivos de asma nas readmissões para o subgrupo de crianças ao qual não foi prescrito um medicamento preventivo de asma na alta hospitalar.

Desenho Estudo de coorte em vários locais com dados administrativos interligados.

**Participantes** — Crianças com idades compreendidas entre os 3 e os 18 anos admitidas por asma num hospital pediátrico terciário, hospital misto pediátrico e de adultos ou hospital regional entre 2017 e 2018.

**Principais medidas de resultados** — Readmissão hospitalar por asma num período de 12 meses.

**Resultados** — Dos 767 participantes, 201 (26,2%) receberam uma nova prescrição ou solicitaram a continuação da utilização de medicamentos para a prevenção da asma. Destes, apenas 91 (45,3%) dispensaram a sua prescrição de alta no prazo de 3 dias ou tinham uma prescrição ativa. Não houve evidência de um efeito protetor da dispensa de medicamentos preventivos de asma na readmissão hospitalar por asma no prazo de 12 meses (OR 1,17, IC 95% 0,69 a 1,97,  $p=0,57$ ). Das 566 crianças a quem não foram prescritos medicamentos preventivos de asma no momento da alta, 269 (47,5%) tiveram uma ou mais prescrições dispensadas na comunidade num período de 12 meses. Os participantes que se encontravam no período de proteção (dispensa de medicação preventiva de asma) tiveram um risco reduzido de readmissão hospitalar por asma (HR 0,61, IC 95% 0,36 a 1,02,  $p=0,06$ ), incluindo crianças em idade pré-escolar (HR 0,48, IC 95% 0,25, 0,93,  $p=0,03$ ) na análise de subgrupo.

**Conclusões** — Verificou-se uma baixa taxa de prescrição e dispensa de medicamentos preventivos de asma na alta hospitalar e não foi encontrado qualquer efeito protetor para o seu impacto nas readmissões. Verificou-se um efeito protetor nas readmissões para a dispensa comunitária de medicamentos preventivos de asma.

## INTRODUCTION

Asthma is a leading cause of chronic illness in industrialised countries and affects both quality of life and health services use.<sup>1</sup> In Australia, asthma is a leading cause of hospitalisations,<sup>2</sup> with a rising hospital readmission rate.<sup>3</sup> A hospital admission is a strong predictor of future readmissions and should prompt a re-evaluation of the child's asthma management.<sup>4,5</sup>

Adherence with long-term medications is often challenging and needs to be considered as part of the intervention plan.<sup>6</sup> A US study reported that a decrease in caregiver report of medication adherence was associated with an increase in asthma readmission despite greater asthma knowledge.<sup>7</sup> Another US study using linked administrative data showed that filling of beta agonist and inhaled

## Key messages

### WHAT IS ALREADY KNOWN ON THIS TOPIC

- Asthma preventer medications are beneficial in preventing exacerbations and reducing hospitalisations in primary school-age children and adolescents.
- Asthma hospital readmission rates are rising.

### WHAT THIS STUDY ADDS

- Fewer than half of the children who were prescribed an asthma preventer at hospital discharge filled their prescription or had an active prescription.
- Prescription of an asthma preventer in the community after a hospital admission was associated with a reduced risk of an asthma hospital readmission.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- This study highlights the importance asthma preventer adherence and regular follow-up in the community.

corticosteroid prescriptions provided at discharge is associated with a reduction in early readmission.<sup>8</sup> To build on these studies, using a similar data linkage methodology to reduce recall bias, we sought to understand asthma preventer dispensing throughout the care journey from hospital discharge through to the community, through an Australian observational cohort study.

To understand the effect of hospital and community asthma preventer adherence on hospital readmissions for asthma, we aimed to (1) describe the dispensing of asthma preventers at hospital discharge and estimate its effect on hospital readmissions within 12 months. For children who were not prescribed an asthma preventer at discharge, we aimed to (2) estimate the effect of community asthma preventer medication dispensing on hospital readmission risk within 12 months. For both aims, we sought to understand the difference in impact on preschool and school-age children.

## PATIENTS AND METHODS

### Participants and consent

The Childhood Asthma RE-admissions study (ANZCTR ID 12619001658101) was a multisite cohort study of children aged 3–18 years admitted

to a tertiary (Royal Children's Hospital), a mixed metropolitan paediatric and adult (Northern Hospital) or regional (University Hospital Geelong) hospital between 1 September 2017 and 31 August 2018. Children who had a discharge diagnosis of asthma or wheeze (International Classification of Diseases 10th Revision codes: J45, J46 or R062) were eligible for diagnosis verification. Children were excluded if they had a comorbid chronic lung disease, uncorrected congenital heart disease or a neuromuscular illness. To verify asthma diagnosis in the study cohort, several procedures were followed (see online supplemental file A).

Caregivers were asked to provide explicit consent to review their child's electronic medical record (EMR) by research staff not involved in clinical care, and to link with records from the Victorian Admitted Episode Dataset (VAED) and Victorian Emergency Minimum Dataset (VEMD). The Australian Institute of Health and Welfare (AIHW) assisted with linkage to Pharmaceutical Benefits Scheme (PBS).

## Data collection

### Description of the data sources

The study team extracted information regarding clinical management, including asthma preventer prescription at the index admission, from the EMR (online supplemental file B). Caregiver survey provided information regarding the caregiver's socioeconomic status and health-related factors (regular general practitioner (GP), comorbidities) (online supplemental file C). VAED recorded all hospital admitted episodes of each participant, including Victorian public and private hospitals. VEMD contains emergency department (ED) attendances at Victorian public hospitals but did not capture attendances at private hospitals. The PBS is a national programme that subsidises medication costs.<sup>9</sup> The PBS data set includes dispensing data on subsidised medications from all community pharmacies, hospital outpatients, discharge dispensing in public and private hospitals in Victoria. Of note, as short-acting beta agonists are available over the counter, their dispensing data are not available on PBS. The study team was provided with drug names, quantity supplied, repeats of prescriptions, specialty of prescribers and dispensing

pharmacies, spanning 12 months preceding the participant's index admission to 12 months following the admission. The PBS does not collect data on diagnosis and indication for prescription. All data exchange and linkage through the Centre of Victorian Data Linkage were done using the Department of Health's secure data exchange tool, a secure password-protected online platform that complies with the relevant legislation requirements to ensure that privacy is protected.

All data sets were analysed within the Secure Unified Research Environment.<sup>10</sup> Data cleaning, management and analyses were done in Stata V.16.0 (StataCorp, Texas).

## Outcome

The primary outcome was hospital readmission with a primary diagnosis of asthma within 12 months of index admission identified through linked data. If the participant's primary caregiver did not provide consent to link with the VAED data set or if the linkage was unsuccessful ( $n=89$ ), the child's EMR at the index hospital was manually reviewed to assess for hospital readmissions at that hospital only.

## Exposures

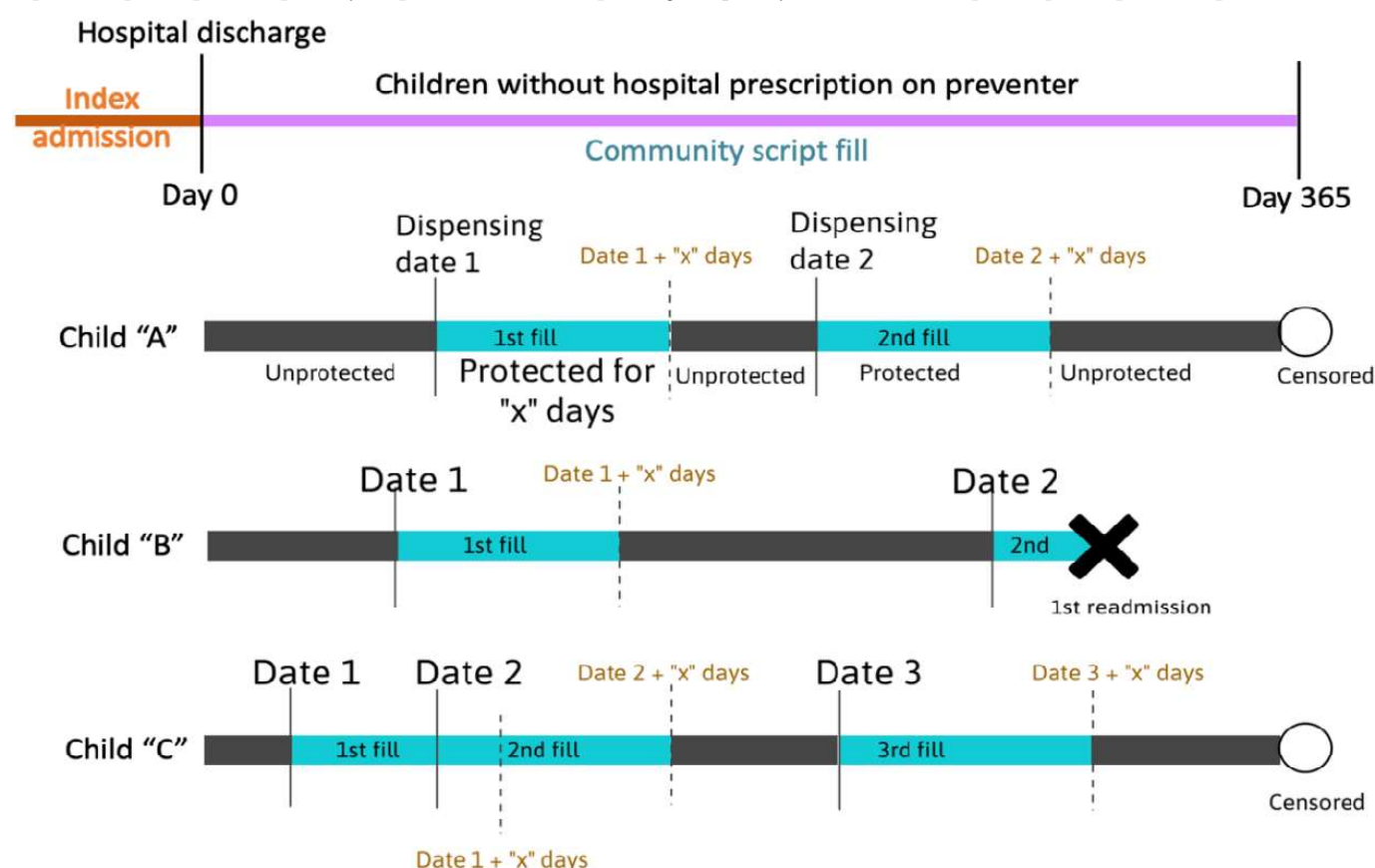
### Discharge asthma preventer dispensed

We defined a participant as having discharge asthma preventer dispensed (any inhaled corticosteroids, combined inhaled corticosteroids and short and long-acting bronchodilators, and leukotriene antagonists) if:

- For participants who were newly prescribed an asthma preventer at the index admission, the medication was dispensed within 3 days after discharge from index admission.
- For participants who were advised to continue with their pre-existing asthma preventer, there was an active prescription prior to the index admission with available quantities after discharge or the medication was dispensed within 3 days after discharge from index admission.

### Community asthma preventer dispensed

Community asthma preventer dispensing varies in time, frequency and number of repeated prescriptions dispensed. We the-



**Figure 1** Example of the time-varying nature of community asthma preventer dispensing.

**Table 1** Demographics of cohort (n=767)

| Mean (SD) or n (%)                                                                                                   | Whole cohort (n=767) | No preventer prescribed (n=566) | Preventer prescribed/asked to continue preventer at discharge (n=201) |
|----------------------------------------------------------------------------------------------------------------------|----------------------|---------------------------------|-----------------------------------------------------------------------|
| Age at index (years)                                                                                                 | 6.2 (3.2)            | 5.7 (2.7)                       | 7.6 (3.8)                                                             |
| Age group (%)                                                                                                        |                      |                                 |                                                                       |
| <6 years                                                                                                             | 476 (62.1)           | 388 (68.6)                      | 88 (43.8)                                                             |
| 6–11 years                                                                                                           | 233 (30.4)           | 154 (27.2)                      | 79 (39.3)                                                             |
| ≥12 years                                                                                                            | 58 (7.6)             | 24 (4.2)                        | 34 (16.9)                                                             |
| Male (%)                                                                                                             | 482 (62.8)           | 348 (61.5)                      | 134 (66.7)                                                            |
| Index hospital (%)                                                                                                   |                      |                                 |                                                                       |
| RCH                                                                                                                  | 511 (66.6)           | 392 (69.3)                      | 119 (59.2)                                                            |
| NH                                                                                                                   | 123 (16.0)           | 85 (15.0)                       | 38 (18.9)                                                             |
| UHG                                                                                                                  | 133 (17.3)           | 89 (15.7)                       | 44 (21.9)                                                             |
| SEIFA quintiles (n=2 missing) (%)                                                                                    |                      |                                 |                                                                       |
| Lowest 20%                                                                                                           | 160 (20.9)           | 113 (20.0)                      | 47 (23.5)                                                             |
| 2nd lowest 20%                                                                                                       | 146 (19.0)           | 109 (19.3)                      | 37 (18.5)                                                             |
| Middle 20%                                                                                                           | 187 (24.4)           | 138 (24.4)                      | 49 (24.5)                                                             |
| 2nd highest 20%                                                                                                      | 147 (19.2)           | 105 (18.6)                      | 42 (21.0)                                                             |
| Highest 20%                                                                                                          | 125 (16.3)           | 100 (17.7)                      | 25 (12.5)                                                             |
| Highest level of primary caregiver education (n=8 missing) (%)                                                       |                      |                                 |                                                                       |
| High school                                                                                                          | 130 (17.1)           | 91 (16.3)                       | 39 (19.5)                                                             |
| Certificate                                                                                                          | 162 (21.3)           | 118 (21.1)                      | 44 (22.0)                                                             |
| Undergraduate degree                                                                                                 | 261 (34.4)           | 194 (34.7)                      | 67 (33.5)                                                             |
| Postgraduate degree                                                                                                  | 206 (27.1)           | 156 (27.9)                      | 50 (25.0)                                                             |
| Interpreter required (n=5 missing) (%)                                                                               | 21 (2.8)             | 19 (3.4)                        | 2 (1.0)                                                               |
| ≥4 newly dispensed asthma preventer medications within 12 months prior to index admission (%)                        | 36 (4.7)             | 11 (1.9)                        | 25 (12.4)                                                             |
| Hospital admission for asthma or wheeze in 12 months prior to index admission (%)                                    | 183 (23.9)           | 120 (21.2)                      | 63 (31.3)                                                             |
| ED presentation 12 months prior to index admission (%)                                                               | 216 (28.2)           | 133 (23.5)                      | 83 (41.3)                                                             |
| Persistent asthma based on HEDIS criteria (yes or no) (%)                                                            | 258 (33.6)           | 160 (28.3)                      | 98 (48.8)                                                             |
| Oxygen use during index admission (%)                                                                                | 110 (14.3)           | 79 (13.9)                       | 122 (60.7)                                                            |
| Intravenous aminophylline or magnesium sulfate, or salbutamol, or methylprednisolone used during index admission (%) | 69 (8.9)             | 37 (6.5)                        | 31 (15.4)                                                             |
| ICU admission during index admission (%)                                                                             | 20 (2.6)             | 7 (1.2)                         | 13 (6.5)                                                              |

ED, emergency department; HEDIS, Healthcare Effectiveness Data and Information Set; ICU, intensive care unit; NH, Northern Hospital; RCH, Royal Children's Hospital; SEIFA, socioeconomic index for area; UHG, University Hospital Geelong.

refore estimated the exposure effect by time periods covered by active prescriptions, described in detail in the Statistical analysis section.

### Confounders

We adjusted for the following confounders in our models: age, sex, socioeconomic index for area (SEIFA), primary caregiver's education, requirement of an interpreter, having a regular GP, comorbidities (atopic, mental health and other conditions), asthma severity defined by Healthcare Effectiveness Data and Information Set (HEDIS) criteria, hospital site, review of inhaler and spacer technique and season of index admission. SEIFA was measured according to postcode of residence using the combined index of relative socioeconomic advantage and disadvantage.<sup>11</sup> We did not define asthma severity based on the more widely used Global Initiative for Asthma (GINA) symptom and severity criteria as 52.1% of participants had insufficient information documented to enable this.<sup>6</sup> Using the HEDIS criteria, persistent asthma was defined as having one of the following in the preceding 12 months: (1) at least four asthma medications dispensed, (2) at least four outpatient GP or specialist visits with a primary diagnosis of asthma and at least two asthma medications dispensed, (3) at least one hospital admission with a primary diagnosis of asthma or (4) at least one ED presentation with a primary diagnosis of asthma.<sup>12</sup>

### Statistical analysis

#### Discharge asthma preventer dispensed

We estimated the effect of discharge asthma preventer dispensing on the risk of hospital readmission within 12 months using a logistic regression model adjusting for potential confounders

listed above. Hospital readmissions within 3 days of the participant's index hospital discharge date were excluded to ensure that the exposure occurred before the event.

#### Community asthma preventer dispensed

To estimate the effect of community preventer dispensing, we only included the subgroup of participants who were discharged without asthma preventers to estimate the effect of community preventer dispensing independent of hospital discharge preventer dispensing. The protected period is defined as the time period during which a participant has a dispensed asthma preventer medication. Therefore, to estimate the impact of community asthma preventer dispensing on hospital readmissions, we identified the protected and unprotected periods for each participant based on date of supply, type of asthma preventer and total amount dispensed at each dispensing from PBS data (figure 1). As PBS data do not contain data on the dose the prescriber intended for the child, we estimated the protected period based on the minimum recommended dose. For example, if an inhaler contains 100 doses and the minimum recommended dose is two puffs per day, the protected period was calculated as 50 days. As readmissions can occur at any time point following the index admission, the participant exited the analysis by censoring after the first hospital readmission or 365 days from index hospital discharge if there were no readmissions. We estimated the HR with 95% CI comparing the risk of hospital readmission between those who were within the protected period of an asthma preventer and those who were not, using Cox proportional hazards regression model adjusted for the confounders described above.

For both aims, we performed a subgroup analysis for preschool (<6 years) and school-age children (≥6) determined a priori supported by GINA guidelines.<sup>6</sup>

### RESULTS

There were 767 children with outcome data available for analysis (figure 2), and 263 (34.3%) were readmitted to a hospital for asthma within 12 months of their index admission. Table 1 summarises the cohort demographics. AIHW was unable to link 16 (2.1%) participants to PBS.

#### Discharge asthma preventer dispensed

At the time of admission, there were 122 children on preventers (71 were primary school and 51 were preschool children). On discharge from the index admission, 79 (10.5%) children were newly prescribed and 122 (16.2%) were requested to continue with their asthma preventers, of whom 113 (56.2%) were primary school children. Only 36 (45.6%) of 79 newly prescribed asthma preventers were dispensed while 55 (45.1%) of 122 participants who were advised to continue their pre-existing asthma preventers had an active prescription or dispensed a prescription within 3 days after discharge. A list of asthma preventers dispensed is listed in online supplemental file D. After adjusting for confounders, there was no evidence for a protective effect of discharge asthma preventer dispensing on hospital readmissions within 12 months and no differences noted on subgroup analysis of preschool and school-age children (table 2). The results were similarly null for hospital readmissions at 28 days (OR 0.36, 95% CI 0.05, 2.85, p=0.3), 90 days (OR 0.73, 95% CI 0.34, 1.57, p=0.4) and 6 months (OR 1.17, 95% CI 0.69, 1.97, p=0.6).

#### Community asthma preventer dispensed

Of the 566 children who were not prescribed asthma preventers at discharge nor advised to continue pre-existing asthma preventer medications, 255 (45.1%) had no asthma preventer dispensed, while 269 (47.5%) had one or more dispensed in the community within 12 months. For children who had asthma preventer protection periods, the median (IQR) of cumulative days under protection was 98 (60–167) days. After adjusting for confounders, children who were in the protected period of asthma preventer dispensing had evidence of a somewhat reduced hazard of a hospital readmission for asthma (table 2). A similar signal of reduced hazard was also seen at 6 months (HR 0.41, 95% CI 0.20, 0.85, p=0.02). On subgroup analysis, the evidence for the protected period of asthma preventer

**Table 2** Effects of discharge and community asthma preventer medication dispensing on hospital readmissions

|                                                        | Entire cohort                          | P value | Preschool children (3–5 years)          | P value | School-age children (6–18 years)        | P value |
|--------------------------------------------------------|----------------------------------------|---------|-----------------------------------------|---------|-----------------------------------------|---------|
| Discharge asthma preventer dispensed*                  | n=751<br>Adjusted OR 1.17 (0.69, 1.97) | 0.57    | n=468†<br>Adjusted OR 1.21 (0.58, 2.53) | 0.62    | n=283†<br>Adjusted OR 1.11 (0.49, 2.47) | 0.81    |
| Community asthma preventer dispensed protected period‡ | n=511<br>Adjusted HR 0.61 (0.36, 1.02) | 0.06    | n=349§<br>Adjusted HR 0.48 (0.25, 0.93) | 0.03    | n=162<br>Adjusted HR 1.05 (0.41, 2.69)  | 0.91    |

\*Logistic regression model adjusted for age, sex, socioeconomic index for area, primary caregiver's education, requirement of an interpreter, having a regular general practitioner, comorbidities, asthma severity, hospital site, review of inhaler and spacer technique and season of index admission.

†88 preschool children and 113 primary school children had hospital discharge asthma preventer dispensed.

‡Cox proportional hazards regression model adjusted for age, sex, socioeconomic index for area, primary caregiver's education, requirement of an interpreter, having a regular GP, comorbidities, asthma severity, hospital site, review of inhaler and spacer technique and season of index admission.

§176 preschool children and 93 primary school children had community asthma preventer dispensed.

in reducing asthma readmission was similar in preschool children (HR 0.39 (0.17, 0.89),  $p=0.02$ ).

## DISCUSSION

In this multisite cohort linkage study, we found low adherence with hospital discharge prescriptions, with fewer than half filling their discharge prescriptions. As asthma preventer medications are easily accessible in the community, most Australian hospitals provide the script on discharge to be dispensed at a community pharmacy. We did not find an association between discharge asthma preventer dispensing and asthma readmissions at 12 months. Our results are similar to those of a large US study of posthospitalisation prescription fills using administrative data sets, which found only a third of patients filled inhaled corticosteroid prescriptions.<sup>8</sup> Highlighting the importance of postdischarge follow-up and protective effects of asthma preventers, we found evidence supporting asthma preventer dispensing in the community in reducing asthma readmissions at 12 months. The reason that a protective effect for asthma preventers was found for children who were dispensed preventers in the community but not for those who were dispensed preventers at discharge may be that community dispensing is a surrogate measure of ongoing follow-up which may include key interventions of asthma management review and self-management education. Furthermore, it is likely that asthma preventers were underprescribed and dispensed at discharge with only about a tenth of children dispensed with a preventer at discharge compared with approximately half in the community. The reason behind this is unclear and important to explore in future studies.

A hospital admission for asthma is considered an indicator of poor control, a strong predictor of future hospitalisation and an important factor to consider in the recommendation of an asthma preventer.<sup>6,13</sup> Despite this, we had low rates of asthma preventer prescription on discharge and high rates of asthma readmission in our study; reasons behind this relatively high readmission rate were previously reported.<sup>14</sup> Our results are similar to an Italian observational study which found only around half of the children received GINA guideline-concordant care after discharge in terms of asthma preventer prescription.<sup>15</sup> An Australian study using a random 10% PBS sample of people aged over 12 years highlights the risk of undertreatment with asthma preventers, which can lead to exposures to high cumulative doses of oral corticosteroids.<sup>16</sup>

Strengths of our study include the use of objective linked data spanning hospital and community asthma preventer dispensing which is not subjected to recall bias.<sup>17</sup> Furthermore, the pragmatic observational design helps to understand the real-life gaps in asthma preventer medication management following discharge. We sampled children from a range of hospital types, meaning our results are likely to generalise across hospitals.

Limitations of our study include the use of medication dispensing as a surrogate for adherence and the lack of information on whether children took the medications. PBS only contains information on the type and amount of asthma preventer medication dispensed, so we did not have data on prescriptions in the community which were not dispensed. We estimated the protected period of the prescription conservatively based on the minimum guideline-recommended dose and therefore may have overestimated the

protection period, thus potentially decreasing the estimated effect of the asthma preventer. We were not able to define severity using GINA due to insufficient information documented in the child's EMR to enable this. We were unable to include environmental factors such as exposure to tobacco smoke, mould and pollution due to incomplete self-reporting and an inability to capture these data accurately. Lastly, we limited our sample to English-speaking caregivers so results may not be generalisable to non-English-speaking families.

Preschool wheeze remains a huge burden on ED and hospital use with limited treatment options for prevention.<sup>18</sup> A trial of asthma preventer medication especially for children requiring a hospital admission or with recurrent bronchodilator responsive wheeze is recommended by international guidelines and what caregivers want in a qualitative study following an asthma admission.<sup>19</sup> Our subgroup analysis supports that preschool children who were prescribed asthma preventer medications in the community and filled their prescriptions were less likely to be readmitted compared with those not on preventer treatment.

Our study highlights the importance of addressing barriers to asthma preventer prescription and dispensing, adherence to guidelines and monitoring this as part of the postdischarge management plan. Until simple interventions known to reduce unplanned ED presentations and hospitalisations are implemented, such as providing in-hand medications on discharge in addition to asthma education,<sup>20</sup> asthma readmissions will likely continue to rise. Similarly, we need to ensure that children who have been admitted with asthma can access a quality medical home (primary care or specialist) that provides regular reviews of asthma control if we are to reduce hospital readmissions.<sup>21</sup>

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**AREXVY**, a única vacina com 94,6% de eficácia contra o VSR, em adultos com  $\geq 60$  anos e com comorbilidades.<sup>1</sup>

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**SAIBA MAIS**

Referências: 1. RCM Arexvy, junho 2023. VSR, vírus sinicial respiratório; IC, intervalo de confiança; DVRI, doença das vias respiratórias inferiores; DPOC, doença pulmonar obstrutiva crônica.

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**GSK**

## ARTIGO ORIGINAL

# Resposta broncodilatadora por técnica de interrupção para orientar o tratamento da pieira pré-escolar

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## RESUMO

**Objetivo** Examinamos as relações entre as características clínicas e a função pulmonar antes e depois do tratamento com corticosteroides inalados (CI) em crianças em idade pré-escolar com pieira e, especificamente, se a medição da resposta ao broncodilatador (RBD) poderia prever o benefício dos CI.

**Desenho** Estudo clínico não aleatorizado com intervenção

**Contexto** Cuidados secundários.

**Doentes** Crianças em idade pré-escolar (2 anos a <6 anos) com pieira recorrente.

**Intervenções** Beta-agonista inalado, CI.

**Medidas de resultado** Medimos a resistência do interruptor (Rint) pré-broncodilatador e pós-broncodilatador e as pontuações dos sintomas às 0 (V1), 4 (V2) e 12 (V3) semanas. Em V2, as pessoas com um nível de sintomas pré-determinado iniciaram o tratamento com CI. O Índice Preditivo de Asma Modificado (IPAm) e a percepção parental da resposta ao broncodilatador foram registados. A resposta aos CI foi definida como uma redução na pontuação diária de sintomas >0,26.

A RBD positiva foi definida como uma queda na Rint de  $\geq 0,26$  kPa.s/L,  $\geq 35\%$  prevista ou  $\geq 1,25$  pontuações Z.

**Resultados** Das 138 crianças recrutadas, 67 completaram o estudo. A média (DP) de Rint pré-broncodilatador em V2 foi de 1,22 (0,35) kPa.s/L, e diminuiu após o início dos CI (V3) para 1,09 (0,33) kPa.s/L ( $p < 0,001$ ), enquanto a média (DP) da pontuação diária de sintomas caiu de 0,56 (0,36) para 0,28 (0,36) após os CI ( $p < 0,001$ ). Uma RBD Rint positiva antes de CI (em V1 e/ou V2), utilizando os três critérios de limiar, foi significativamente associada à resposta a CI nas pontuações dos sintomas em V3 ( $p < 0,05$ ). O IPAm não foi significativamente associado à resposta aos CI e a percepção dos pais da resposta ao broncodilatador não foi relacionada com a RBD Rint medida.

**Conclusões** A RBD Rint pode ser útil para selecionar quais as crianças em idade pré-escolar com pieira que poderão beneficiar de CI.

## INTRODUCTION

Wheezing in preschool children (roughly aged 2–5 years) is a major clinical problem, and one of the most common causes of primary care consultations, emergency department visits and hospital admissions.<sup>1</sup> The majority of school-age children with asthma are managed in primary care, because reliable treatments are available, and accepted national and international guidelines exist to guide both treatment and referral to secondary care.<sup>2–3</sup> The same cannot be said of preschool wheezing, which many primary care physicians continue to feel insecure in managing, and where guidelines acknowledge a lack of evidence.<sup>2–3</sup> Treatments in this age group are less predictably effective, probably because preschool children who wheeze make up a heterogeneous group.<sup>4–5</sup> They include some children who have asthma as recognised and defined in the school-age child, but they also

## Key messages

### What is the key question?

► Preschool children with wheeze are a heterogeneous group, and it is difficult clinically to decide which children would benefit from regular inhaled corticosteroids (ICS). Bronchodilator response (BDR) using interrupter resistance (Rint) can separate young children with asthma from healthy children.

### What is the bottom line?

► Wheezy preschool children, who have a higher than threshold Rint response to bronchodilator, are more likely to also respond clinically to starting ICS therapy.

### Why read on?

► Measuring Rint BDR may help clinicians decide which children to treat with ICS.

include children who probably have constitutionally narrow airways, do not respond to asthma treatment, and tend to become asymptomatic by school age.<sup>4–6</sup> These two groups have been distinguished retrospectively in epidemiological studies,<sup>5</sup> but are difficult to distinguish clinically at presentation. Clinically, wheezy preschool children who wheeze can be classified into ‘episodic viral wheeze’ and ‘multiple-trigger wheeze’,<sup>4</sup> but these phenotypes are not stable and children migrate between them over the preschool period.<sup>6</sup> Scoring systems to predict the likelihood of preschool wheeze persisting as school-age asthma have been proposed,<sup>7–8</sup> but are insufficiently sensitive to be useful clinically.<sup>9</sup>

A major contributing factor to the difficulty in diagnosis and treatment of preschool wheezy children has been the lack of information about lung function. In the diagnosis of asthma in adults and school-age children, measurement of lung function including bronchodilator response (BDR) is widely advocated.<sup>2–3,10</sup> A number of lung function measurements are feasible in infants and preschool children, but many require sedation and/or are very time-consuming. Interrupter resistance (Rint) has the advantages of being relatively easily measured using commercially available, handheld equipment, and of an extensive knowledge base of normal values and variability in preschool children.<sup>11–15</sup> Although baseline Rint (like baseline spirometry) is not sufficiently sensitive for reliable diagnosis of asthma,<sup>16</sup> BDR measured by Rint is able to separate preschool children with asthma from normal controls with reasonably good sensitivity and specificity,<sup>17–18</sup> and is correlated with methacholine responsiveness in preschool children

with chronic cough.<sup>19</sup> Rint has also been able to delineate a dose-response curve to salbutamol in preschool children similar to that using forced expiratory volume in 1 second (FEV<sub>1</sub>) in older children.<sup>20</sup> However, there is a lack of evidence to support routine measurement of Rint (and other preschool lung function measures) in clinical practice.

The aim of this study was to establish the potential usefulness of Rint BDR measurement in guiding therapeutic decision-making in preschool children with recurrent wheeze. The primary objective was to determine whether a significant BDR measured using Rint is predictive of clinical response to inhaled corticosteroids (ICS). Secondary objectives were (A) To establish the most discriminant threshold for BDR and (B) To establish the between-occasion repeatability of Rint BDR.

## METHODS

### Participants

We recruited preschool children aged 2 years to <6 years with a history of at least three episodes of wheeze (high-pitched whistling sound) in the previous 6 months, at least one documented by a healthcare professional. Children were recruited from outpatient clinics, hospital emergency departments and inpatient wards. We did not include children who had already been given regular preventative asthma therapy (ICS or montelukast), nor children with a history of significantly preterm birth (less than 34 weeks gestation) or congenital cardiorespiratory disease. Full informed consent was sought from parent or guardian.

### Maternal influenza vaccination

The full study consisted of three visits: visit 1 (V1)—baseline, visit 2 (V2)—+4 weeks and visit 3 (V3)—+12 weeks. At V1, baseline clinical data were collected including the items needed to calculate a modified Asthma Predictive Index (mAPI).<sup>8</sup> All Rint measurements were performed outside an acute respiratory episode. Rint was measured before and 15 min after administering 400 µg of salbutamol via metered dose inhaler and spacer (RintBDR1). Rint was measured using a MicroRint device (MicroMedical/CareFusion), in accordance with published guidelines.<sup>15</sup> Brief (100 ms) airway occlusions were performed during tidal breathing with cheeks supported, occluding at peak tidal expiratory flow. Flow was measured immediately prior to occlusion, and driving pressure for Rint measurement was derived by back-extrapolation from the pressure transient. Pressure transients were inspected visually for acceptability according to agreed criteria,<sup>15</sup> and Rint was calculated as the median value of at least five acceptable occlusions.

We examined three different published criteria for determining a clinically significant BDR:

1. An absolute fall in Rint of at least 0.26 kPa.s/L.<sup>17</sup>
2. A fall in Rint of at least 35% of the predicted value.<sup>18</sup>
3. A fall in Rint of at least 1.25 Z Scores.<sup>17</sup>

If a child was unable to complete a valid Rint measurement at V1, further coaching was provided and Rint measurement was attempted again at V2.

Parents were then issued with the Paediatric Asthma Caregiver Diary (PACD), a symptom diary which has been validated in wheezy preschool children,<sup>21</sup> and asked to record symptoms daily for 4 weeks in order to establish baseline symptom frequency. In addition, at V1, parents were asked to respond to the simple binary question 'Does your child's blue reliever inhaler (Salbutamol/Ventolin) help?'

At V2, the PACD was reviewed, and Rint was again measured before and after salbutamol (RintBDR2). At this stage, children whose PACD record did not meet the minimum predetermined symptom frequency (symptoms and/or bronchodilator use on at least 2 days per week) did not continue further in the study. Children who met the symptom threshold were given standard dose ICS therapy administered by metered dose inhaler and spacer: beclomethasone (Clenil Modulite, Chiesi) 200 µg twice daily or fluticasone (Flixotide, GlaxoSmithKline) 100 µg twice daily. Baseline asthma-related quality of life was recorded using the Paediatric Asthma Caregiver Quality of Life Questionnaire (PACQLQ),<sup>22</sup> and

parents were asked to resume recording the PACD 4 weeks before V3.

At V3, 8 weeks after V2, the PACD was collected, Rint and Rint BDR were again measured (RintBDR3), the PACQLQ was recorded, and skin-prick testing was performed to four common aeroallergens: house dust mite, grass pollen, cat and dog dander.

The daily symptom score from the PACD was used to determine whether there had been a clinical response to starting ICS. A clinically important response to starting ICS was defined as a reduction in daily symptom score (PACD) of more than 0.26,<sup>23</sup> comparing the 4 weeks before V2 and the 4 weeks before V3.

## Analysis

Outcome data were compared between visits, and in the case of Rint measurements, before and after bronchodilator. Analysis was performed using Stata (Stata Corporation, College Station, Texas, USA). Data were examined for normality using the Shapiro-Wilk test, and paired comparisons performed using t-test or Wilcoxon, as appropriate. Rint BDR repeatability was examined using Bland-Altman analysis.<sup>24</sup> Association between categorical outcomes was assessed using Pearson's  $\chi^2$  test.

## RESULTS

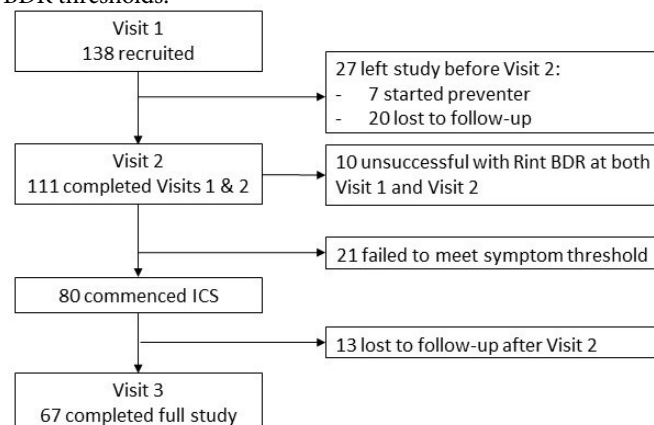
Figure 1 shows the numbers of children completing each stage of the study and reasons for dropping out. A total of 138 children met the initial inclusion criteria and were recruited: 121 at the Brighton site and 17 at the Paris site. Eighty children commenced a trial of ICS at V2, but 13 were lost to follow-up: results are presented for the 67 children who attended all three visits.

Table 1 summarises the clinical characteristics of these children. The majority of children had been admitted to hospital for wheezing episodes and were clinically atopic, and over 75% had a positive mAPI.

Table 2 summarises the prebronchodilator and postbronchodilator Rint values, PACD Scores and PACQLQ Scores at each visit. None of the children had previous experience of lung function measurement. Of the 67 children completing the full study, 12 were unable to achieve satisfactory Rint measurements at V1, but all succeeded at V2. One child did not have Rint measurements performed at V3 because they had just completed a course of oral corticosteroids for an acute wheezing episode.

There was a highly significant decrease in prebronchodilator Rint for the group overall from V2 to V3 (ie, 8 weeks after starting ICS), and a trend towards decrease in postbronchodilator Rint—only significant for Rint expressed as Z Score. Both PACD Scores (decrease) and PACQLQ Scores (increase) improved significantly from V2 to V3.

Using the raw value threshold ( $\geq 0.26$  kPa.s/L) tended to give the highest number of positive BDR responses at each visit compared with the other two thresholds, but this difference was not significant at any visit, and the proportion of children with positive BDR was not significantly different between the visits for any of the BDR thresholds.



**Figure 1** Flow diagram of study participation. BDR, bronchodilator response; ICS, inhaled corticosteroid.

**Table 1** Clinical characteristics of children completing the full study (n=67)

| Variables                                                    | Median (range) or number (%) |
|--------------------------------------------------------------|------------------------------|
| Age (months)                                                 | 37 (24 to 71)                |
| Sex M/F                                                      | 38 (57) / 29 (43)            |
| Number of wheezy episodes in previous 6 months               | 3 (3 to 12)                  |
| Number of previous hospitalisations                          |                              |
| =0                                                           | 29 (43)                      |
| =1                                                           | 11 (17)                      |
| ≥2                                                           | 27 (40)                      |
| Parents' perception of efficacy of short-acting beta agonist |                              |
| Yes                                                          | 53 (79)                      |
| No                                                           | 12 (18)                      |
| Unsure                                                       | 2 (3)                        |
| Children with personal atopy (any)                           | 42 (63)                      |
| Children with                                                |                              |
| Eczema                                                       | 36                           |
| Allergic rhinitis                                            | 12                           |
| Food allergy                                                 | 5                            |
| Children with family history of atopy (parent or sibling)    | 53 (79)                      |
| Children with at least one skin-prick test positive          | 27 (40)                      |
| Children with skin-prick test positive to                    |                              |
| HDM                                                          | 23                           |
| Cat                                                          | 12                           |
| Dog                                                          | 7                            |
| Grass                                                        | 6                            |

**Between-visit repeatability of Rint BDR**

Figure 2 shows a Bland-Altman graph of the difference between BDR at V1 and V2 plotted against the mean BDR across the two visits, for each of the 55 children who had BDR measurements at both visits. The mean difference (V1–V2) was +0.08 kPa.s/L, with limits of agreement (–2 SD and +2 SD) from –0.57 kPa.s/L to +0.73 kPa.s/L. However, it is also instructive and perhaps more meaningful clinically to look at how consistently children met the thresholds for significant BDR across the two visits: these data are shown in table 3.

**Relationship between BDR and response to ICS**

There was a significant association between recording a positive BDR at either V1 or V2 and having an improvement in daily symptom score of more than 0.26, using all three BDR thresholds. Table 4 shows the p value of this association, and the predictive value of each threshold for a symptom response to ICS. All three BDR thresholds were also significantly associated with a decrease in prebronchodilator Rint between V2 and V3 (p=0.005 for ≥0.26 kPa.s/L, p=0.013 for ≥35%pred, p=0.005 for ≥1.25Z). By contrast, neither mAPI nor atopy (defined as at least one positive skin-prick test) showed any association with response to ICSs.

The decrease in Rint between V2 and V3 was similarly frequent among children with or without symptom response to ICS: 24/35 (69%) decrease in Rint (10/35 (29%) decrease above the BDR threshold) and 19/31 (61%) decrease in Rint (7/31 (23%) decrease above the BDR threshold), respectively.

Figure 3 shows individual values for Rint BDR at V2 and V3, by raw Rint value (figure 3A), %predicted (figure 3B) and Z score (figure 3C).

**DISCUSSION**

There is now an extensive literature describing and standardising techniques to measure lung function in preschool children,<sup>15</sup> and a sizeable body of knowledge on the application of these techniques in

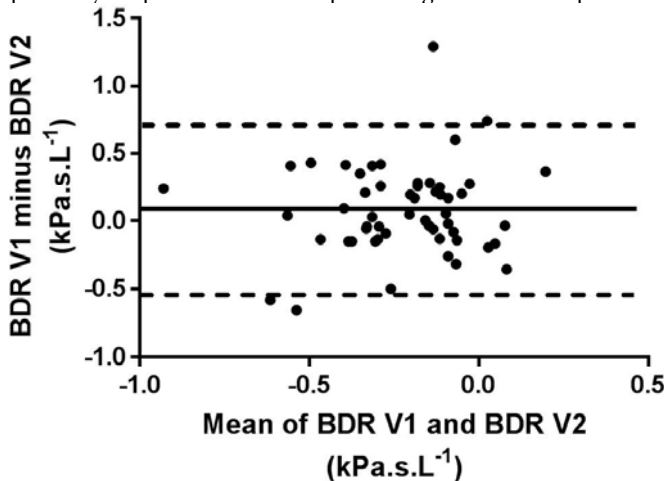
**Table 2** Rint measurements, symptom and quality of life scores at the three study visits

|                                               | Visit 1       | Visit 2       | Visit 3         |
|-----------------------------------------------|---------------|---------------|-----------------|
| Children with successful Rint measurement (n) | 55            | 67            | 66              |
| Baseline measurements                         |               |               |                 |
| Pre-BD Rint, kPa.s/L                          | 1.13 (0.37)   | 1.22 (0.35)   | 1.09 (0.33) *   |
| Pre-BD Rint, % predicted                      | 121 (38)      | 127 (31)      | 114 (31) *      |
| Pre-BD Rint, Z Score                          | +0.68 (1.28)  | +0.96 (1.07)  | +0.47 (1.11) *  |
| Postbronchodilator measurements               |               |               |                 |
| Post-BD Rint, kPa.s/L                         | 0.95 (0.25)†  | 0.95 (0.29)†  | 0.89 (0.26)†    |
| Post-BD Rint, % predicted                     | 101 (26) †    | 99 (26)†      | 93 (25) †       |
| Post-BD Rint, Z score                         | –0.02 (0.99)† | –0.11 (1.01)  | –0.37 (1.04)†‡  |
| Significant Rint reversibility                |               |               |                 |
| BDR ≥0.26 kPa.s/L                             | 18 (32.7)     | 35 (52.2)     | 24 (36.4)       |
| BDR ≥35% predicted                            | 13 (23.6)     | 22 (32.8)     | 20 (30.3)       |
| BDR ≥1.25 Z Score                             | 16 (29.1)     | 25 (37.3)     | 21 (31.8)       |
| Symptom and quality of life scores            |               |               |                 |
| PACD Score for the 4 weeks prior to visit     |               | 0.56 (0.36)   | 0.28 (0.36) *   |
| PACQLQ Score                                  |               | 5.5 (1.9–7.0) | 6.4 (2.6–7.0) * |

Results are number (%) or mean (SD); for PACQLQ Score, median (range).  
\*Visit 3 versus visit 2, p<0.001 .  
†Post-BD versus pre-BD, p<0.001.  
‡Visit 3 versus visit 2, p<0.05.  
BD, bronchodilator; BDR, bronchodilator response; PACD, Paediatric Asthma Caregiver Diary; PACQLQ, Paediatric Asthma Caregiver Quality of Life Questionnaire; Rint, interrupter resistance.

a range of respiratory disorders.<sup>25</sup> Preschool lung function measurements have been used, for example, to compare children with recurrent wheeze or diagnosed asthma with healthy children,<sup>17 18 26</sup> to follow-up children with different patterns of preschool wheeze,<sup>27–29</sup> or as outcome measures in clinical trials of therapy.<sup>30–32</sup> However, to our knowledge, this is the first prospective study to assess the potential role of preschool lung function testing to guide therapeutic decisions in recurrently wheezy young children.

Our findings agree with previous studies<sup>30–32</sup> in showing that treating wheezy preschool children with ICS is associated with an improvement in mean airway resistance, but this response is very variable whether measured by lung function or by symptoms, with some children not improving at all. We have demonstrated that a positive BDR (measured using Rint) was associated with a subsequent therapeutic response to ICS. This was in contrast to clinically based predictors such as mAPI and atopy, which in this study were not predictive of response to ICS. The sensitivity and specificity of positive BDR for predicting a clinical response to



**Figure 2** Bland-Altman plot of repeatability of bronchodilator response (BDR) measurements, showing mean difference (full line) and limits of agreement (dashed lines). V1, visit 1; V2, visit 2.

**Table 3** Consistency of demonstrating BDR at V1 and V2

|                           | V1 and V2 | V1 or V2 | Neither |
|---------------------------|-----------|----------|---------|
| BDR $\geq 0.26$ kPa.s/L   | 13        | 19       | 23      |
| BDR $\geq 35\%$ predicted | 4         | 21       | 30      |
| BDR $\geq 1.25$ Z score   | 7         | 20       | 28      |

BDR, bronchodilator response; V1, visit 1; V2, visit 2.

ICS were modest, with the threshold  $\geq 1.25$  Z score having perhaps the most promising characteristics. Interestingly, this Rint BDR threshold showed better sensitivity and specificity for predicting ICS response than a 10% FEV<sub>1</sub> BDR threshold in school-age asthmatics.<sup>33</sup>

We also demonstrated, and quantified, the degree of variability of Rint BDR between occasions. This variability is not surprising, particularly in preschool children who tend to have an episodic pattern of symptoms. Even in school-age children using FEV<sub>1</sub> BDR, the Childhood Asthma Management Program (CAMP) Study showed huge between-occasion variability in BDR, with only a small minority of children (5%) consistently meeting the BDR threshold,<sup>34</sup> while up to a third showed BDR at any one visit. For this study, the predetermined requirement was that a child demonstrate BDR on one occasion: this is in keeping with the criteria for diagnosing school-age asthma for most clinical trials, and in recent guidelines.<sup>10</sup> Our results (table 3) suggest that the raw value and Z Score thresholds give greater consistency in classification than the % predicted threshold. Because of this variability, we would suggest measuring BDR on two clinic visits prior to starting ICS, if using presence or absence of BDR to help decision making.

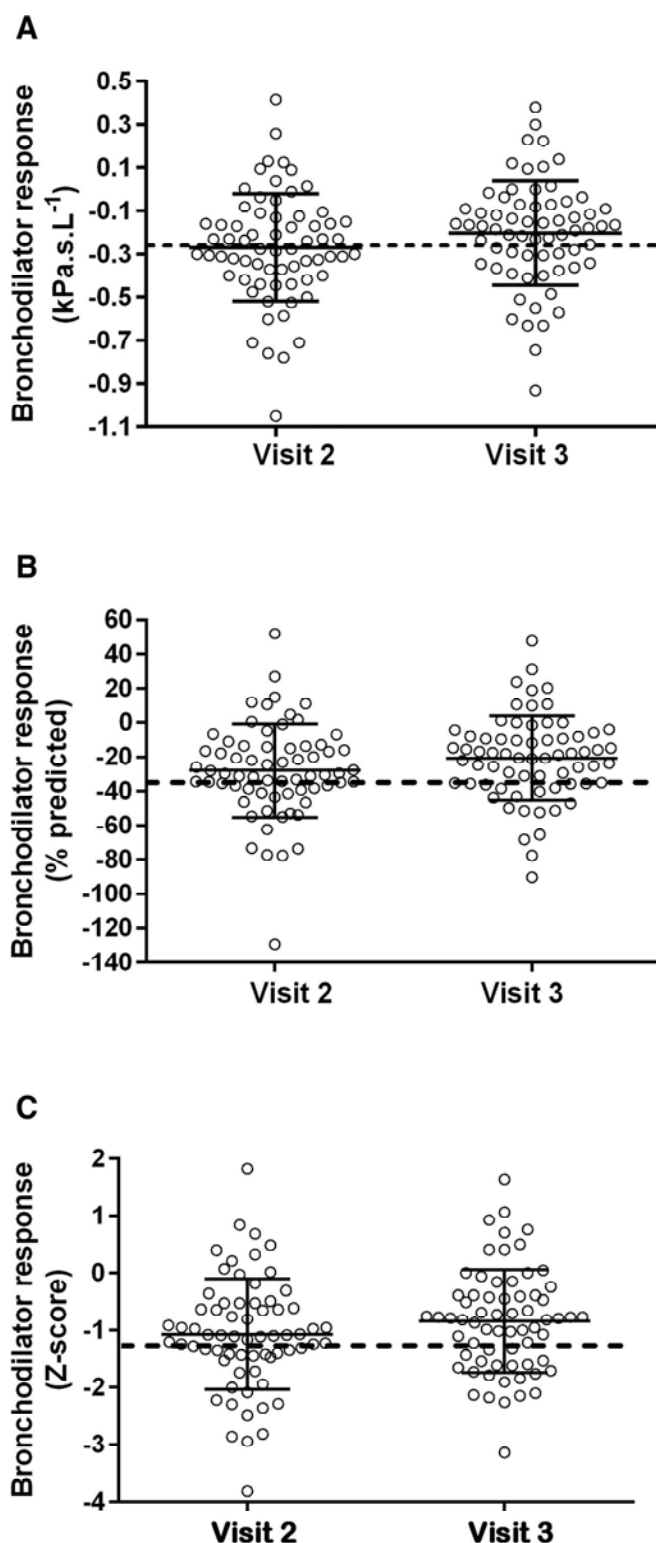
Limitations of the study include the relatively small size, and the choice of the outcome measure to denote a response to ICS. We selected the only symptom diary which has been validated in preschool children,<sup>21</sup> but the minimum important difference for this tool has not been determined: we therefore chose as our threshold the change in symptom score which had been reported in a previous clinical trial in a similar population.<sup>23</sup> Although we used a disease-specific quality of life measure (PACQLQ), this has not been validated in preschool children. It could be argued that reduction in exacerbations might be a preferable outcome, but this would have required a much longer duration of study. We did not use a physiological measure (reduction in Rint after ICS treatment) as our primary outcome, but it is interesting to note that this was also associated with Rint BDR. We did not include a control group of healthy children. Rint has been extensively studied in wheezy and healthy children,<sup>11 12 14</sup> and it has similar repeatability in both groups.<sup>16 35</sup>

One could argue that there is no need for a physiological measurement to help decide which preschool wheezy children to treat with ICS. There is no evidence that early initiation of ICS improves long-term lung function,<sup>36</sup> and therefore one could simply wait for a clear clinical picture of asthma to emerge and/or for the child to be able to perform spirometry. However, in the meantime the child and family will have endured preventable symptoms and impaired life quality. Alternatively, one could commence a trial of ICS on all children with significant wheezing. The problems with this approach are that there is no adequate objective measure of response, and that once commenced, ICS tend to be continued long-term, with the child drifting into an implicit diagnosis of asthma. As in older children, absence of BDR does not preclude a trial of ICS, but a positive BDR is helpful objective evidence of reactive airways likely to respond to ICS.

**Table 4** Predictive value of BDR using the three thresholds

| BDR threshold       | V3 outcome             | P value | Sensitivity | Specificity | Positive predictive value | Negative predictive value | Likelihood ratio |
|---------------------|------------------------|---------|-------------|-------------|---------------------------|---------------------------|------------------|
| $\geq 0.26$ kPa.s/L | Symptom Score $> 0.26$ | 0.02    | 0.74        | 0.55        | 0.64                      | 0.65                      | 1.63             |
| $\geq 35\%$ pred    | Symptom Score $> 0.26$ | 0.032   | 0.59        | 0.68        | 0.67                      | 0.60                      | 1.82             |
| $\geq 1.25$ Z       | Symptom Score $> 0.26$ | 0.019   | 0.65        | 0.65        | 0.67                      | 0.63                      | 1.82             |

BDR, bronchodilator response; V3, visit 3.



**Figure 3** Graphs showing Rint BDR for individual children at V2 and V3, by raw value (3A), %predicted (3B) and Z Score (3C). In each graph the solid lines and whiskers show mean and SD, while the dashed lines show the threshold for clinical BDR significance. BDR, bronchodilator response; Rint, interrupter resistance; V2, visit 2; V3, visit 3.

It is interesting, but not surprising, that Rint BDR persisted in many children at V3 despite treatment with ICS. Persistence of BDR in children with asthma on ICS is well recognised — in the CAMP Study<sup>34</sup> up to a third of children continued to show BDR despite ICS treatment, and Rint shows a higher frequency of BDR than spirometry.<sup>37</sup> Neither this nor the CAMP Study monitored adherence, and this could have been a factor.

In conclusion, we have demonstrated proof of concept that measuring BDR using a tidal breathing measure of respiratory resistance could be helpful in deciding which wheezy preschool children are likely to benefit from ICS therapy. Further studies are needed: to replicate our findings in a larger group and over a longer period; looking at exacerbations as well as daily symptom scores; and using other preschool lung function techniques such as oscillometry or specific airway resistance.

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**Patient consent for publication** Not applicable.

**Ethics approval** This study involves human participants and was approved by Brighton West NHS Research Ethics Committee (IRAS 07/H1111/106) in the UK and by the Comité de Protection des Personnes (CPP) Île-de-France 1 (n° 0911968) in France. Participants gave informed consent to participate in the study before taking part.

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Não perca mais tempo.**

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#### DPOC, doença pulmonar obstrutiva crônica

**Referências:** 1. Riltrava Aerosphere 5 microgramas/7,2 microgramas/160 microgramas, suspensão pressurizada para inalação [Resumo das Características do Medicamento]. AstraZeneca AB, SE-151 85 Södertälje Suécia; abril 2022. Acedido em [www.infarmed.pt](http://www.infarmed.pt) em outubro 2022. 2. Bevespi Aerosphere 5 microgramas/7,2 microgramas, suspensão pressurizada para inalação [Resumo das Características do Medicamento]. AstraZeneca AB, SE-151 85 Södertälje Suécia; agosto 2022. Acedido em [www.infarmed.pt](http://www.infarmed.pt) em outubro 2022. 3. Ho T-W, Tsai Y-J, Ruan S-Y, et al. In-Hospital and One-Year Mortality and Their Predictors in Patients Hospitalized for First-Ever Chronic Obstructive Pulmonary Disease Exacerbations: A Nationwide Population-Based Study. *Bai C, editor. PLoS ONE*. 2014 Dec;9(12):e114866.

#### Informações essenciais compatíveis com o Resumo das Características do Medicamento

**Bevespi Aerosphere 7,2 microgramas/5 microgramas, suspensão pressurizada para inalação.** Cada dose única (dose libertada que sai do aplicador bucal) contém 9 microgramas de brometo de glicopirrônio, equivalente a 7,2 microgramas de glicopirrônio, e 5 microgramas de fumarato de formoterol di-hidratado. Isto corresponde a uma dose calibrada de 10,4 microgramas de brometo de glicopirrônio, equivalente a 8,3 microgramas de glicopirrônio, e 5,8 microgramas de fumarato de formoterol di-hidratado. **Indicações terapêuticas:** Bevespi Aerosphere é indicado como tratamento broncodilatador de manutenção para o alívio de sintomas em doentes adultos com doença pulmonar obstrutiva crônica (DPOC). **Posologia e modo de administração:** **Posologia:** A dose recomendada é duas inalações duas vezes por dia (duas inalações de manhã e duas inalações à noite). Os doentes devem ser aconselhados a não fazer mais de 2 inalações duas vezes por dia. Se for omitida uma dose, esta deve ser tomada assim que for possível e a dose seguinte deve ser tomada no horário habitual. Não deve tomar-se uma dose a dobrar para compensar uma dose esquecida. **Populações especiais:** **Idosos:** Não é necessário qualquer ajuste de dose em doentes idosos. **Compromisso renal:** Bevespi Aerosphere pode ser utilizado na dose recomendada em doentes com compromisso renal ligeiro a moderado. Em doentes com compromisso renal grave ou com doença renal em fase terminal com necessidade de diálise, só deve ser utilizado se o benefício esperado for superior ao risco potencial. **Compromisso hepático:** Bevespi Aerosphere pode ser utilizado na dose recomendada em doentes com compromisso hepático ligeiro a moderado. Não existem dados relevantes sobre a utilização de Bevespi Aerosphere em doentes com compromisso hepático grave e o medicamento deve ser utilizado com precaução nestes doentes. **População pediátrica:** Não existe utilização relevante de Bevespi Aerosphere em crianças e adolescentes (com idade inferior a 18 anos) para a indicação de DPOC. **Modo de administração:** Utilização por via inalatória. **Instruções de utilização:** Ao acionar Bevespi Aerosphere, um volume de suspensão é expelido do recipiente pressurizado a alta velocidade. Quando o doente inala através do aplicador bucal ao mesmo tempo que aciona o inalador, a substância segue o ar inspirado para as vias respiratórias. Os doentes devem ser instruídos sobre a técnica de inalação correta. É importante instruir o doente para: Ler com atenção as instruções de utilização no folheto informativo, que se encontra dentro da embalagem de cada inalador. Não utilizar o inalador se o agente excicante, contido na bolsa de alumínio, tiver vazado da sua embalagem. Preparar o inalador agitando-o e acionando-o quatro vezes para o ar antes da primeira utilização ou duas vezes quando o inalador não tenha sido utilizado há mais de sete dias, tenha sido exposto a temperaturas baixas ou tenha caído. Para obter uma deposição pulmonar adequada das substâncias ativas, o carregamento da dose tem de ser coordenado com a inalação. Doentes com dificuldade em coordenar o carregamento da dose com a inspiração podem utilizar Bevespi Aerosphere com uma câmara expansora para garantir a administração adequada do produto. Foi demonstrada compatibilidade com a câmara expansora Aerochamber Plus Flow-Vu. **Contra-indicações:** Hipersensibilidade às substâncias ativas ou a qualquer um dos excipientes. **Advertências e precauções especiais de utilização:** **Asma:** Bevespi Aerosphere não deve ser utilizado no tratamento da asma. **Broncospasmo paradoxal:** Se ocorrer broncospasmo paradoxal, o tratamento com o medicamento deve ser interrompido e devem ser considerados outros tratamentos. **Não indicado para utilização em situações agudas:** Bevespi Aerosphere não é indicado para o tratamento de episódios agudos de broncospasmo, isto é, como terapêutica de alívio. **Efeitos cardiovasculares:** Podem ser observados efeitos cardiovasculares, após a administração de antagonistas dos receptores muscarínicos e simpaticomiméticos, incluindo glicopirrônio ou formoterol. Bevespi Aerosphere deve ser utilizado com precaução em doentes com doenças cardiovasculares graves, tais como cardiopatia isquémica, taquiarritmias ou insuficiência cardíaca grave. Recomenda-se também precaução em doentes com tireotoxicose ou com prolongamento do intervalo QTc conhecido ou suspeito. **Hipocalcemia:** Os agonistas  $\beta_2$ -adrenérgicos podem causar hipocalcemia significativa, o que pode aumentar a suscetibilidade para arritmias cardíacas. A diminuição do potássio sérico é normalmente transitória, não necessitando de suplementação. Em doentes com DPOC grave, a hipocalcemia pode ser potenciada por hipoxia e tratamento concomitante. **Hiperglicemia:** A inalação de doses elevadas de agonistas  $\beta_2$ -adrenérgicos pode provocar o aumento da glicose plasmática. **Atividade anticolinérgica:** Devido à sua atividade anticolinérgica, Bevespi Aerosphere deve ser utilizado com precaução em doentes com hiperplasia da próstata sintomática, retenção urinária ou glaucoma de ângulo fechado. **Compromisso renal:** Como o glicopirrônio é excretado predominantemente por via renal, os doentes com compromisso renal grave (depuração de creatinina <30 ml/min), incluindo aqueles com doença renal em fase terminal com necessidade de diálise, apenas devem ser tratados com Bevespi Aerosphere se o benefício esperado superar o risco potencial. **Compromisso hepático:** Em doentes com compromisso hepático grave, Bevespi Aerosphere só deve ser utilizado se o benefício esperado superar o risco potencial. Estes doentes devem ser monitorizados para potenciais reações adversas. **Interações medicamentosas e outras formas de interação:** **Interações farmacocinéticas:** O potencial para interações metabólicas é considerado baixo. Como o glicopirrônio é eliminado principalmente por via renal, podem ocorrer potencialmente interações medicamentosas com medicamentos que afetam os mecanismos de excreção renal. **Interações farmacodinâmicas:** Outros antimuscarínicos e simpaticomiméticos: A coadministração de Bevespi Aerosphere com outros medicamentos contendo anticolinérgicos e/ou agonistas  $\beta_2$ -adrenérgicos de longa duração de ação não foi estudada e não é recomendada uma vez que poderá potenciar as reações adversas conhecidas dos antagonistas muscarínicos ou dos agonistas  $\beta_2$ -adrenérgicos inalados. Não existe evidência clínica de interações quando utilizado concomitantemente com outros medicamentos para a DPOC, incluindo broncodilatadores  $\beta_2$ -adrenérgicos de curta duração de ação, metilxantinas e esteróides orais e inalados. **Hipocalcemia induzida por fármacos:** O tratamento concomitante com derivados da metilxantina, esteróides ou diuréticos não poupadores de potássio pode potenciar o possível efeito hipocalcémico inicial dos agonistas  $\beta_2$ -adrenérgicos, pelo que se recomenda precaução na sua utilização concomitante. **Bloqueadores  $\beta_2$ -adrenérgicos:** Os bloqueadores  $\beta_2$ -adrenérgicos (incluindo colírios) podem atenuar ou inibir o efeito dos agonistas  $\beta_2$ -adrenérgicos, tal como o formoterol. O uso simultâneo de bloqueadores  $\beta_2$ -adrenérgicos não seletivos ou seletivos deve ser evitado, a não ser que existam razões determinantes para a sua utilização. Se forem necessários bloqueadores  $\beta_2$ -adrenérgicos (incluindo colírios), dê-se preferência a bloqueadores  $\beta_2$ -adrenérgicos cardiosseletivos, embora também estes devam ser administrados com precaução. **Outras interações farmacodinâmicas:** Bevespi Aerosphere deve ser administrado com precaução em doentes que estejam a ser tratados com medicamentos conhecidos por prolongar o intervalo QTc. **Fertilidade, gravidez e aleitamento:** **Gravidez:** Não existem dados sobre a utilização de Bevespi Aerosphere em mulheres grávidas. Bevespi Aerosphere só deve ser utilizado durante a gravidez se os benefícios esperados superarem os potenciais riscos. **Amamentação:** Não é conhecido se o glicopirrônio ou o formoterol são excretados no leite humano. A administração de Bevespi Aerosphere a mulheres que estão a amamentar só deve ser considerada se o benefício esperado para a mãe for superior a qualquer possível risco para o bebé. **Fertilidade:** Considera-se pouco provável que Bevespi Aerosphere, administrado na dose recomendada, afete a fertilidade no ser humano. **Efeitos indesejáveis:** **Frequentes:** Ansiedade, Cefaleia, Tonturas, Boca seca, Náuseas, Espasmos musculares, Infecção do trato urinário, Dor torácica. **Pouco frequentes:** Reações de hipersensibilidade, incluindo erupção cutânea e prurido, Hiperglicemia, Agitação, Irrequietude, Insónia, Tremor, Taquicardia, Palpitações, Arritmias cardíacas (fibrilhação

auricular, taquicardia supraventricular e extra-sístoles), Retenção urinária. Pede-se aos profissionais de saúde que notifiquem quaisquer suspeitas de reações adversas através do Sítio da internet: <http://www.infarmed.pt/web/infarmed/submissaoar> (preferencialmente) ou através dos seguintes contactos: Direção de Gestão do Risco de Medicamentos: (Tel.: +351217987373; Linha do Medicamento: 800222444 (gratuita); E-mail: [farmacovigilancia@infarmed.pt](mailto:farmacovigilancia@infarmed.pt)). **Titular da Autorização de Introdução no Mercado:** AstraZeneca AB, SE-151 85 Södertälje, Suécia. **Representante local do Titular da Autorização de Introdução no Mercado:** Tecnimed - Sociedade Técnico-Medicinal, S.A., Rua da Tapada Grande, n.º 2, Abrunheira, 2710-089 Sintra. Informações revistas em agosto 2022. **Para mais informações deverá contactar o representante local do Titular da Autorização de Introdução no Mercado. Medicamento sujeito a receita médica. Medicamento compartilhado pelo Escalão B (69% de comparticipação no regime geral e 84% de comparticipação no regime especial). Versão 1.0 (agosto 2022).**

#### Informações essenciais compatíveis com o Resumo das Características do Medicamento

**Riltrava Aerosphere 5 microgramas/7,2 microgramas/160 microgramas, suspensão pressurizada para inalação.** Cada dose única (dose libertada que sai do aplicador bucal) contém 5 µg de fumarato de formoterol di-hidratado, 9 µg de brometo de glicopirrónio, equivalente a 7,2 µg de glicopirrónio e 160 µg de budesonida. Isto corresponde a uma dose calibrada de 5,3 µg de fumarato de formoterol di-hidratado, 9,6 µg de brometo de glicopirrónio, equivalente a 7,7 µg de glicopirrónio e 170 µg de budesonida. **Indicações terapêuticas:** Riltrava Aerosphere é indicado como tratamento de manutenção em doentes adultos com DPOC moderada a grave, que não estão adequadamente tratados com uma associação de um corticosteroide inalado e um agonista beta2 de longa duração de ação ou uma associação de um agonista beta2 de longa duração de ação e um antagonista muscarínico de longa duração de ação. **Posologia e modo de administração:** **Posologia:** A dose recomendada e máxima é de 2 inalações 2x/dia (2 inalações de manhã e 2 inalações à noite). Se for omitida uma dose, esta deve ser tomada assim que for possível e a dose seguinte deve ser tomada no horário habitual. Não se deve tomar uma dose a dobrar para compensar uma dose esquecida. **Populações especiais:** **Idosos:** Não é necessário qualquer ajuste de dose em doentes idosos. **Compromisso renal:** Este medicamento pode ser utilizado na dose recomendada em doentes com compromisso renal ligeiro a moderado. Pode também ser utilizado na dose recomendada em doentes com compromisso renal grave ou com doença renal em fase terminal com necessidade de diálise, apenas se o benefício esperado for superior ao risco potencial. **Compromisso hepático:** Este medicamento pode ser utilizado na dose recomendada em doentes com compromisso hepático ligeiro a moderado. Pode também ser utilizado na dose recomendada em doentes com compromisso hepático grave, o medicamento deve ser utilizado apenas se o benefício esperado for superior ao risco potencial. **População pediátrica:** Não existe utilização relevante deste medicamento em crianças e adolescentes (com idade inferior a 18 anos) para a indicação da DPOC. **Modo de administração:** Para utilização por via inalatória. **Instruções de utilização:** De forma a assegurar uma administração correta do medicamento, o médico ou outro profissional de saúde deve demonstrar ao doente como utilizar corretamente o inalador, e deve monitorizar regularmente a técnica de inalação do doente. O doente deve ser aconselhado a ler com atenção o Folheto Informativo e seguir as instruções de utilização conforme indicado no mesmo. Ao acionar Riltrava Aerosphere, um volume de suspensão é expelido do recipiente pressurizado. Quando o doente inala através do aplicador bucal ao mesmo tempo que aciona o inalador, a substância segue o ar inspirado para as vias respiratórias. Os doentes que têm dificuldade em coordenar o acionamento com a inalação podem utilizar Riltrava Aerosphere com uma câmara expansora para garantir a administração adequada do medicamento. Pode ser utilizado com câmaras expansoras incluindo o Aerochamber Plus FlowVu. **Contraindicações:** Hipersensibilidade às substâncias ativas ou a qualquer um dos excipientes. **Advertências e precauções especiais de utilização:** **Não indicado para utilização em situações agudas.** Este medicamento não é indicado para o tratamento de episódios agudos de broncospasma, isto é, como terapêutica de alívio. **Broncospasma paradoxal:** A administração de formoterol/glicopirrónio/budesonida pode produzir broncospasma paradoxal com sibilos e dispneia imediatamente após a administração e pode ser potencialmente fatal. O tratamento com este medicamento deve ser imediatamente interrompido se ocorrer broncospasma paradoxal. O doente deve ser avaliado e instituído tratamento alternativo, se necessário. **Deterioração da doença:** Recomenda-se que o tratamento com este medicamento não seja interrompido abruptamente. Se os doentes não considerarem o tratamento eficaz, devem manter o tratamento, mas tem de se procurar aconselhamento médico. O aumento da utilização de broncodilatadores de alívio indica um agravamento do quadro clínico subjacente e justifica uma reavaliação da terapêutica. A deterioração rápida e progressiva nos sintomas da DPOC é potencialmente fatal e o doente deve ser submetido a avaliação médica urgente. **Efeitos cardiovasculares:** Podem ser observados efeitos cardiovasculares, tais como arritmias cardíacas, p.ex. fibrilação auricular e taquicardia, após a administração de antagonistas dos receptores muscarínicos e simpaticomiméticos, incluindo glicopirrónio e formoterol. Este medicamento deve ser utilizado com precaução em doentes com doença cardiovascular grave não controlada e clinicamente significativa, tal como cardiopatia isquémica instável, enfarte agudo do miocárdio, cardiomiopatia, arritmias cardíacas, e insuficiência cardíaca grave. Recomenda-se também precaução ao tratar doentes com prolongamento do intervalo QTc (QTc > 450 milissegundos para homens ou > 470 milissegundos para mulheres), conhecido ou suspeito, quer seja congénito ou induzido por medicamentos. **Efeitos sistémicos com corticosteroides:** Podem ocorrer efeitos sistémicos com qualquer corticosteroide inalado, particularmente em doses elevadas prescritas por longos períodos de tempo. Estes efeitos são muito menos prováveis de ocorrer com o tratamento por inalação do que com corticosteroides orais. Os efeitos sistémicos possíveis incluem síndrome de Cushing, manifestações Cushingoides, supressão suprarrenal, diminuição da densidade mineral óssea, cataratas e glaucoma. Devem ser considerados efeitos potenciais na densidade óssea especialmente com a administração de doses elevadas durante longo período de tempo em doentes com fatores de risco coexistentes para osteoporose. **Perturbações visuais:** Podem ser notificadas perturbações visuais com a utilização sistémica e tóxica de corticosteroides. Se um doente apresentar sintomas tais como visão turva ou outras perturbações visuais, o doente deve ser encaminhado para um oftalmologista para avaliação de possíveis causas que podem incluir cataratas, glaucoma ou doenças raras, tais como CRSC, que foram notificadas após a utilização de corticosteroides sistémicos e tópicos. **Transfusão de terapêutica oral:** Recomenda-se atenção especial nos doentes que fazem a transição de esteróides orais, uma vez que podem continuar em risco de compromisso da função suprarrenal durante um período de tempo considerável. Os doentes que necessitam de terapêutica com doses elevadas de corticosteroides ou tratamento prolongado com a dose mais elevada recomendada de corticosteroides inalados, podem estar igualmente em risco. Estes doentes podem apresentar sinais e sintomas de insuficiência suprarrenal quando expostos a stress grave. Deve ser considerada cobertura adicional com corticosteroides sistémicos durante períodos de stress ou cirurgia eletiva. **Pneumonia em doentes com DPOC:** Tem sido observado um aumento na incidência de pneumonia, incluindo pneumonia que requer hospitalização, nos doentes com DPOC a receberem corticosteroides inalados. Existe alguma evidência de risco aumentado de pneumonia com o aumento da dose de esteroide, não tendo sido demonstrado de forma conclusiva nos diversos estudos. Não existe evidência clínica conclusiva para diferenças dentro da mesma classe na magnitude do risco de pneumonia entre os medicamentos contendo corticosteroides inalados. Os médicos devem continuar alerta para o possível desenvolvimento de pneumonia em doentes com DPOC pois as características clínicas de tais infeções sobrepõem-se aos sintomas das exacerbações da DPOC. Os fatores de risco para pneumonia em doentes com DPOC incluem tabagismo atual, idade avançada, IMC baixo e DPOC grave. **Hipocalcemia:** A hipocalcemia potencialmente grave pode resultar da terapêutica com agonistas-β. Estes têm o potencial de produzir acontecimentos cardiovasculares adversos. Recomenda-se precaução especial na DPOC grave, pois esse efeito pode ser potencializado pela hipoxia. A hipocalcemia também pode ser potencializada pelo tratamento concomitante com outros medicamentos que podem induzir hipocalcemia, tais como derivados de xantinas, esteróides e diuréticos. **Hiperglicemia:** A inalação de doses elevadas de agonistas β<sub>2</sub>-adrenérgicos pode provocar o aumento da glucose plasmática. A glicemia deve ser monitorizada durante o tratamento de acordo com as orientações estabelecidas para doentes com diabetes. **Condições coexistentes:** Este medicamento deve ser utilizado com precaução em doentes com tireotoxicose. **Atividade anticolinérgica:** Devido à sua atividade anticolinérgica, este medicamento deve ser utilizado com precaução em doentes com hiperplasia da próstata sintomática, retenção urinária ou glaucoma de ângulo fechado. Os doentes devem ser informados sobre os sinais e sintomas do glaucoma de ângulo fechado e devem ser informados para interromper a utilização deste medicamento e contactar o seu médico imediatamente, caso algum destes sinais ou sintomas se desenvolvam. Não é recomendada a administração concomitante deste medicamento com outros medicamentos contendo anticolinérgicos. **Compromisso renal:** Como o glicopirrónio é excretado predominantemente por via renal, os doentes com compromisso renal grave (depuração de creatinina <30 ml/min), incluindo aqueles com doença renal em fase terminal com necessidade de diálise, apenas devem ser tratados com este medicamento se o benefício esperado superar o risco potencial. **Compromisso hepático:** Em doentes com compromisso hepático grave, este medicamento só deve ser utilizado se o benefício esperado superar o risco potencial. Estes doentes devem ser monitorizados para potenciais reações adversas. **Interações medicamentosas e outras formas de interação:** **Interações farmacodinâmicas:** Prevê-se que o tratamento em associação com inibidores potentes do CYP3A, por exemplo itraconazol, cetoconazol, inibidores de protease do VIH e medicamentos que contêm cobicistate, aumente o risco de efeitos indesejáveis sistémicos, e deve ser evitado, a não ser que o benefício seja superior ao risco aumentado de reações adversas aos corticosteroides sistémicos, nesse caso os doentes devem ser monitorizados para reações adversas aos corticosteroides sistémicos. Este facto é de relevância clínica limitada em tratamentos de curta duração (1-2 semanas). Como o glicopirrónio é eliminado principalmente por via renal, podem ocorrer potencialmente interações medicamentosas com medicamentos que afetam os mecanismos de excreção renal. **Interações farmacodinâmicas:** **Outros antimuscarínicos e simpaticomiméticos:** A administração concomitante deste medicamento com outros medicamentos contendo anticolinérgicos e/ou agonistas β<sub>2</sub>-adrenérgicos de longa duração de ação não foi estudada e não é recomendada uma vez que poderá potenciar as reações adversas conhecidas dos antagonistas muscarínicos ou dos agonistas β<sub>2</sub>-adrenérgicos inalados. A utilização concomitante de outros medicamentos beta-adrenérgicos pode ter efeitos potencialmente aditivos; portanto é necessário precaução quando outros medicamentos beta-adrenérgicos são prescritos concomitantemente com formoterol. **Hipocalcemia induzida por medicamentos:** A hipocalcemia pode aumentar a disposição para arritmias em doentes que são tratados com glicosídeos digitálicos. **Bloqueadores β-adrenérgicos:** Os bloqueadores β-adrenérgicos (incluindo colírios) podem atenuar ou inibir o efeito do formoterol. O uso simultâneo de bloqueadores β-adrenérgicos deve ser evitado, a não ser que o benefício esperado ultrapasse o risco potencial. Se forem necessários bloqueadores β-adrenérgicos, dá-se preferência a bloqueadores β-adrenérgicos cardiosseletivos. **Outras interações farmacodinâmicas:** O tratamento concomitante com quinidina, disipiramida, procainamida, anti-histamínicos, inibidores da monoamina oxidase, antidepressivos tricíclicos e fenotiazinas pode prolongar o intervalo QT e aumentar o risco de arritmias ventriculares. Além disso, L-dopa, L-tirosina, oxitocina e álcool podem prejudicar a tolerância cardíaca aos beta2-simpaticomiméticos. O tratamento concomitante com inibidores da monoamina oxidase, incluindo medicamentos com propriedades semelhantes como furazolidona e procarbazina, pode dar origem a reações hipertensivas. Existe um risco elevado de arritmias em doentes a receberem anestesia concomitante com hidrocarbonetos halogenados. **Fertilidade, gravidez e aleitamento:** A administração deste medicamento a mulheres grávidas só deve ser considerada se o benefício esperado para a mãe justificar o potencial risco para o feto. A administração deste medicamento a mulheres que estão a amamentar só deve ser considerada se o benefício esperado para a mãe for superior a qualquer possível risco para a criança. Considera-se pouco provável que este medicamento administrado na dose recomendada, afete a fertilidade no ser humano. **Efeitos indesejáveis:** **Frequentes:** Candidíase oral; Pneumonia; Hiperglicemia; Ansiedade; Insónia; Cefaleia; Palpitações; Disfonia; Tosse; Náuseas; Espasmos musculares; Infecção do trato urinário. **Pouco frequentes:** Hipersensibilidade; Depressão; Agitação; Irrequietude; Nervosismo; Tonturas; Tremor; Angina de peito; Taquicardia; Arritmias cardíacas (fibrilação auricular, taquicardia supraventricular e extrasístoles); Irritação da garganta; Broncospasma; Boca seca; Equimose; Retenção urinária; Dor torácica. **Muito raros:** Sinais ou sintomas de efeitos sistémicos de glucocorticóides, por exemplo supressão suprarrenal; Comportamento anormal. **Desconhecido:** Angioedema; Visão turva; Cataratas; Glaucoma. Pede-se aos profissionais de saúde que notifiquem quaisquer suspeitas de reações adversas através do Sítio da internet: <http://www.infarmed.pt/web/infarmed/submissaoar> (preferencialmente) ou através dos seguintes contactos: Direção de Gestão do Risco de Medicamentos: (Tel.: +351 21 798 73 73; Linha do medicamento: 800 222 444 (gratuita); E-mail: [farmacovigilancia@infarmed.pt](mailto:farmacovigilancia@infarmed.pt)). **Titular da Autorização de Introdução no Mercado:** AstraZeneca AB, SE-151 85 Södertälje, Suécia. **Representante local do Titular da Autorização de Introdução no Mercado:** Tecnimed - Sociedade Técnico-Medicinal, S.A., Rua da Tapada Grande, n.º 2, Abrunheira, 2710-089 Sintra. Informações revistas em abril 2022. **Para mais informações deverá contactar o representante local do Titular da Autorização de Introdução no Mercado. Medicamento sujeito a receita médica. Medicamento compartilhado pelo Escalão B (69% de comparticipação no regime geral e 84% de comparticipação no regime especial). Versão 1.1 (abril 2022).**

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## ARTIGO ORIGINAL

# Melhor prescrição de antimicrobianos pediátricos com um aplicativo para smartphone: um estudo intervenção antes e depois

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## RESUMO

**Introdução** As crianças têm um elevado consumo de antimicrobianos, o que exige uma tomada de decisões complicada por parte dos prescritores. Apesar disso, as intervenções de gestão de antimicrobianos (GAM) não são frequentemente transpostas para a medicina pediátrica. Script é uma aplicação para smartphone (app) lançada em Auckland, na Nova Zelândia, para apoiar a tomada de decisões dos prescritores de antimicrobianos. O objetivo foi melhorar a adesão às diretrizes clínicas locais existentes tanto para infeções em adultos como pediátricas.

**Métodos** Prospectivamente, foram recolhidas e avaliadas as prescrições de antimicrobianos nos serviços de internamento e de urgência de modo a determinar a adesão às diretrizes. Foram recolhidos dados de base sobre a prescrição e comparados com a prescrição a 4 meses e a 1 ano após o lançamento da aplicação. As prescrições foram classificadas como "adequadas" ou "inadequadas" pelos investigadores. A classificação foi efetuada sem ter em conta o momento da prescrição relativamente à intervenção.

**Resultados** Após o lançamento da app Script, a adesão às diretrizes aumentou significativamente de 241 de 348 (69%) prescrições antimicrobianas classificadas como adequadas durante o período de referência para 301 de 359 (83%) após 4 meses ( $p<0,0001$ ). Esta melhoria em relação aos valores iniciais manteve-se ao fim de um ano, com 263 de 323 (81%) de adesão ( $p<0,001$ ). Ao fim de um ano, esta melhoria pôde ser demonstrada separadamente para as prescrições médicas, cirúrgicas e do serviço de urgência.

**Conclusão** Verificou-se uma melhoria significativa e sustentada na adesão às diretrizes antimicrobianas pediátricas após a introdução de uma aplicação de apoio à prescrição. A necessidade de procurar orientação para as doses de antimicrobianos devido aos cálculos baseados na idade e no peso em pediatria pode significar que as intervenções de GAM, como o apoio à decisão e as ferramentas de prescrição, são particularmente adequadas para a prescrição pediátrica.

## INTRODUCTION

The emergence of antimicrobial resistance (AMR) is a global public health threat<sup>1</sup> and has been attributed to overuse and misuse of antibiotics.<sup>2</sup> Consumption of antibiotics is particularly high in childhood. By the age of 5 years, antibiotic exposure in New Zealand children is near universal at 97%.<sup>3</sup> Starship Children's Hospital (SCH) is New Zealand's national tertiary children's hospital. Annual point prevalence surveys have shown that over 40% of SCH inpatients are prescribed antimicrobials.<sup>4</sup> While excess antimicrobial use contributes to AMR, inappropriate undertreatment of infections also causes patient harm. Adherence to antimicrobial guidelines has been shown to be associated with reduced mortality outcomes and shortened length of hospital stay.<sup>5</sup> Paediatric prescribing can be complex: choices are affected by age and weight, availability and palatability of oral formulations, and reported antibiotic allergies. De-

## Key messages

### What is the key question?

- Antimicrobial guidelines improve patient outcomes and reduce mortality, and smartphone applications (apps) are used widely in medicine.
- Apps have been shown to improve antimicrobial guideline adherence in prescribing for adults in some situations; however, the effect has been variable.

### What is the bottom line?

- This is the first study to demonstrate sustained improvement in paediatric antimicrobial guideline adherence using a smartphone app.
- Improvement was shown across paediatric medicine, surgery and emergency department prescribing.

### Why read on?

- These results suggest that smartphone technology can improve antimicrobial prescribing in the paediatric setting.
- This provides support for the implementation of similar projects in other paediatric healthcare settings.

spite high consumption and complex prescribing in paediatrics, antimicrobial stewardship (AMS) interventions have traditionally focused on adult prescribing with infrequent translation into the care of children.

SCH maintains a library of paediatric clinical guidelines<sup>6</sup> which are open access, web based and used nationally across New Zealand. At the time of designing the application (app), there were approximately 250 clinical guidelines; 15% contained antimicrobial advice and many others provided antimicrobial stewardship and allergy guidance. All guidelines which include antimicrobials are reviewed or written by the paediatric infectious diseases service and approved by the hospital AMS committee. Between 2015 and 2019, annual inpatient point prevalence surveys within SCH demonstrated around 65% adherence to these guidelines when prescribing antibiotics, antivirals and antifungals.<sup>4</sup>

In 2016, Auckland City Hospital, an attached adult hospital, launched the Script app. Script was an antimicrobial prescribing smartphone app with algorithmic decision support for use in adults. The effect of Script on adult prescribing was modest; community-acquired pneumonia guideline adherence improved from 19% to 27% of prescriptions ( $p=0.04$ ), but there was no significant improvement in adherence to urinary tract infection guidelines,



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47%–50% ( $p=0.49$ ).<sup>7</sup> Similarly, a smartphone app in the UK improved antibiotic prescribing on adult surgical but not medical wards.<sup>8</sup> A Canadian study in adults found clinically (but not statistically) significant improvements in appropriate antibiotic prescribing on medical wards after the introduction of a smartphone app, although prescribing on surgical wards worsened.<sup>9</sup> Thus far, there have been no equivalent data for paediatrics. In March 2019, the Script app was extensively updated to include paediatric guidelines and algorithms.

## Objective

We hypothesised that the introduction of guidelines presented on a smartphone app would improve prescriber adherence to existing clinical guidelines in a tertiary paediatric hospital.

We aimed to prospectively evaluate inpatient and emergency department antimicrobial prescribing for adherence to both local hospital and community antimicrobial guidelines. We compared prescribing before and after the introduction of the app.

## Design

We performed a pre-intervention and post-intervention study that compared the proportion of antimicrobial prescriptions that were adherent to guidelines.

## Setting

SCH is New Zealand's national children's hospital. It is a 219-bed tertiary hospital with specialist medical and surgical services including paediatric intensive care, cardiothoracic surgery, oncology and transplant services. The hospital provides secondary paediatric care to approximately 46 000 patients in Auckland and tertiary care to the nearly 1 million children of New Zealand.<sup>10</sup>

## Intervention

SCH clinical guidelines were mapped onto decision trees for 30 common clinical diagnoses where antimicrobials are used. The trees incorporated information about age, history of penicillin allergy, ability to take tablets and known colonisation with resistant organisms, such as methicillin resistant *Staphylococcus aureus* (MRSA). Answers to these questions were used to provide treatment choices (figure 1).

In March 2019, the Script for Paediatrics app was made freely available in New Zealand on Apple and GooglePlay stores with paediatric guidelines and decision support. In the 12 months following the launch, the combined adult and paediatric app was downloaded by more than 4000 users and in the second year, the

number of users increased to 7500. On average, the paediatric guidelines are accessed 1875 times per month. Script for Paediatrics users have not only been based at SCH but in paediatric centres throughout New Zealand.

## Study of the intervention

Pre-intervention (baseline) data were collected in study period one which occurred between 7 January and 17 February 2019. Script for Paediatrics was launched in March 2019. Post-intervention study period two occurred between 1 July and 18 August 2019. Data collection for post-intervention study period three occurred between 1 March and 5 April 2020. During each data collection period, all SCH inpatient prescription charts were reviewed every 2–3 days. All patients with current antimicrobial prescriptions at 08:00 on the collection day were included as were all children's emergency department (CED) discharges from the preceding 24 hours. Prescription charts and clinical notes were reviewed for each eligible patient to determine the empirical antimicrobial or antimicrobials first prescribed, and the indication for each antimicrobial prescription. Data were collected, in an Excel spreadsheet, until the prespecified numbers were collected. Hospital inpatient and CED discharge lists were used to ensure data were collected for all patients who met criteria on the audit dates. No data were collected for patients who were on antimicrobials outside the prespecified audit days.

There were no other new AMS interventions introduced at SCH during the study period. Other AMS activities within the hospital continued as normal, including biweekly AMS ward rounds, use of a restricted antimicrobial list and the existing web-based Starship Clinical Guidelines continued to be available. Clinical prescribers were not informed of the audit, but the Script app was widely advertised, with posters, emails and at hospital grand rounds.

## Inclusion and exclusion criteria

Children up to 15 years of age, both inpatient and those discharged from CED, were included in the data collection, if empirical antimicrobials were being given during the study period days. Exclusions at the time of data collection included (1) antimicrobials for an indication not covered by the clinical guidelines and (2) targeted prescribing for known pathogens. The neonatal intensive care unit was excluded because preterm dosing and guidelines were not included in the app. Children receiving antimicrobials initiated in referring hospitals were also excluded. Where antimicrobials were initiated in the community prior to admission, the first antimicrobial prescription in hospital was used for analysis.

Figure 1 Examples of application output for community-acquired pneumonia. IV, intravenous.

## Main outcome measures

### Data collection

The empirical antimicrobial agent and prescription details including route, dose and frequency were collected by paper-based chart review. Additional information including indication, antibiotic allergy, renal dysfunction, weight and age was also collected from the patients' records. Data were anonymised and stored on a secure hospital computer, on a password-protected spreadsheet.

### Analysis

$\chi^2$  tests were used to compare the proportion of antimicrobial prescriptions adherent to the guideline during each study period and where sample sizes were small, a Fisher's exact test was used instead. Sample size calculations indicated that 292 participants in each time period were required to detect a 10% difference with 80% power and a 95% CI. Calculations were performed in R.<sup>11</sup>

Data were graded based on the clinical indication recorded in the clinical record at the time of antimicrobial initiation (table 1). This grading was in accordance with the National Antimicrobial Prescribing Survey.<sup>4</sup> Two graders, a paediatric infectious diseases fellow and an AMS pharmacist (SP and NP), reviewed the data. They independently graded each antimicrobial prescription while blinded to study period. These grades were then compared using study codes. There were five cases of grading discordance. In these cases, the study team infectious diseases paediatricians (RW, EW, LV, EJB), also blinded to study period, made a final consensus determination based on the data collected. When the prescription exactly matched the Script app guidance, prescriptions were considered 'optimal'. Prescriptions were considered 'adequate' when they matched alternative local guidance that was widely available online, including national formulary dosing, alternative options within SCH guidelines or community guidelines. Relevant online guidelines were accessed at the start and end of each study period so any changes in guidance could be considered. When guidelines changed (one guideline), a prescription that followed guidance applicable during any of the study periods was considered adequate. Those classified as 'optimal' or 'adequate' were deemed to be appropriate prescribing, all other categories were deemed to be inappropriate. High-risk errors were prescriptions of an antimicrobial to which the patient had a potentially life-threatening allergy, inadequate treatment of a potentially life-threatening infection or a potentially clinically significant overdose of medication. For full definitions and examples of grading classifications, see table 1. We used the Standards for Quality Improvement Reporting Excellence checklist when writing our report.<sup>12</sup>

## RESULTS

This study analysed 1030 individual medication prescriptions from 823 patient episodes. Inpatients made up 713 (70%) of prescriptions and the remaining 317 (30%) were children discharged from CED. At baseline, prescriber adherence to guidelines was 69% (239 of 346 prescriptions). During study period two, 4 months after the launch of the app, adherence increased to 84% (304 of 365,  $p<0.001$ ). In study period three, 1 year after the launch, appropriate prescribing was sustained at 81% (263 of 323,  $p<0.001$ ) (see table 2 for full results). Prescribing errors considered 'high risk' decreased from 7 of 346 (0.02%) to 1 of 323 (0.008%) between study periods one and three; however, this did not reach statistical significance ( $p=0.07$ ). Appropriate antimicrobial use increased between study period one and study period two in medical prescribing (78%–90%,  $p=0.005$ ) and emergency department prescribing (59%–79%,  $p=0.006$ ). These improvements were sustained in both medical and emergency department prescribing at study period three with surgical prescribing now also showing improvement when compared with baseline (63%–76%,  $p=0.045$ ). The greatest improvement in appropriate prescribing, at 1-year follow-up, was seen in emergency department discharges (19% of prescriptions) followed by surgical patients (13%) and the smallest change was seen in medical patients (11%). Overall, 'optimal' prescribing which exactly followed the Script app increased (47%–62%,  $p<0.001$ ); this improvement did not derive from a reduction in prescribing

**Table 1** Grading classifications for comparison of antimicrobial prescriptions with the Script app and local clinical guidelines<sup>6</sup>

| Classification | Definition                                                                                                                                                                                   | Example(s)                                                                                                                                        |
|----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|
| Optimal        | The prescription matched the SCH clinical guidelines/Script app exactly                                                                                                                      | Choice, route and dosage correct (within 10%)                                                                                                     |
| Adequate       | The prescription did not meet criteria for optimal prescribing but used an acceptable alternative local or national guideline (eg, community guidelines, New Zealand Formulary for children) | Oral flucloxacillin suspension prescribed for cellulitis (cefalexin recommended for palatability)                                                 |
| Suboptimal     | Mild or non-life-threatening allergy mismatch OR spectrum, dose or route excessive                                                                                                           | Co-amoxiclav prescribed for uncomplicated community-acquired pneumonia                                                                            |
| Inadequate     | Not appropriate for the indication and unlikely to treat, OR choice, dosage or route insufficient                                                                                            | Cellulitis treated with amoxicillin                                                                                                               |
| Unnecessary    | No antimicrobial required                                                                                                                                                                    | Antibiotics prescribed for presumed viral illness                                                                                                 |
| High risk      | Life-threatening allergy mismatch OR inadequate treatment of a life-threatening infection OR overdose considered dangerous                                                                   | Use of penicillin when previous penicillin anaphylaxis documented OR inadequate dose of aciclovir in encephalitis OR large overdose of gentamicin |

Adapted from the National Antimicrobial Prescribing Survey.<sup>4</sup>  
app, application; SCH, Starship Children's Hospital.

consistent with other guidance ('adequate prescribing'), but from multiple different incorrect prescribing grades, demonstrating that this was not merely changing which guidance was followed, but led to overall improvement in following any guidance.

## DISCUSSION

This is the first study in paediatrics to examine antimicrobial guideline adherence following introduction of a smartphone app and demonstrated a significant and sustained improvement across all services. Targeted studies evaluating a single indication for antimicrobials such as bacterial gastroenteritis<sup>13</sup> have shown significant improvement with use of prescribing or guideline apps. However, when evaluating the broader use of antimicrobials in hospitalised adults, prior New Zealand and international research have inconsistent results, some of borderline statistical significance.<sup>7–9</sup> Our study of paediatric antimicrobial prescribing demonstrated sustained improvement across medical and surgical services and among emergency department discharges. The improvement in emergency department discharge prescriptions is particularly significant as these patients' prescriptions are not reviewed on subsequent ward rounds or on AMS rounds.

The high impact of the Script for Paediatrics app is likely to reflect the complexities of drug dosing in paediatrics, resulting in increased usage of guidelines by prescribers. Prior research showed that 13% of prescriptions written for children contain errors and this rate is higher than that seen in adult prescribing.<sup>14</sup> Individualised prescribing based on factors such as age and weight reflects the need to compensate for the pharmacokinetic and pharmacodynamic changes seen throughout childhood and adolescence.<sup>15–19</sup> Medication adherence in children is also highly dependent on drug formulation and palatability and can be incorporated into decision support when prescribing oral antimicrobials. These differences can be challenging to memorise, resulting in the need for prescribers to use guidelines more often than prescribers for adult patients.

Prescribers favour smartphone app-based guidance over more traditional formats,<sup>20</sup> with smartphones commonly being carried during hospital duties. Another benefit of mobile apps is the ability to remind prescribers of the role of allergy, oral palatability or resistant organism colonisation when prescribing.

There were several limitations in this quality improvement study. The indication for each prescription was derived from documenta-

**Table 2** Grading of appropriate antimicrobial prescribing before and after launch of the Script app by hospital service

|                                                                   | Baseline  | Post-intervention |           | P value         | P value         |
|-------------------------------------------------------------------|-----------|-------------------|-----------|-----------------|-----------------|
|                                                                   | Period 1  | Period 2          | Period 3  | Period 1 versus | Period 1 versus |
|                                                                   | Total (%) | Total (%)         | Total (%) | period 2        | period 3        |
| Children's emergency department prescriptions                     |           |                   |           |                 |                 |
| Total analysed                                                    | 69        | 125               | 123       |                 |                 |
| Optimal                                                           | 24 (35)   | 67 (54)           | 66 (54)   | 0.02*           | 0.02*           |
| Adequate                                                          | 17 (25)   | 32 (26)           | 33 (27)   | >0.9            | 0.9             |
| Suboptimal                                                        | 13 (19)   | 12 (10)           | 11 (9)    | 0.1             | 0.08            |
| Inadequate                                                        | 5 (7)     | 6 (5)             | 13 (11)   | 0.5             | 0.4             |
| Unnecessary                                                       | 8 (12)    | 8 (6)             | 0 (0)     | 0.3             | <0.001*         |
| High risk                                                         | 2 (3)     | 0 (0)             | 0 (0)     | 0.1             | 0.1             |
| Overall appropriate prescribing†                                  | 41 (59)   | 99 (79)           | 99 (80)   | 0.006*          | 0.003*          |
| Medical (general paediatrics and paediatric subspecialties)       |           |                   |           |                 |                 |
| Total analysed                                                    | 161       | 165               | 92        |                 |                 |
| Optimal                                                           | 83 (52)   | 99 (60)           | 66 (72)   | 0.2             | 0.003*          |
| Adequate                                                          | 43 (27)   | 50 (30)           | 16 (17)   | 0.6             | 0.1             |
| Suboptimal                                                        | 15 (9)    | 6 (4)             | 8 (9)     | 0.06            | >0.9            |
| Inadequate                                                        | 13 (8)    | 6 (4)             | 2 (2)     | 0.1             | 0.09            |
| Unnecessary                                                       | 2 (1)     | 2 (1)             | 0 (0)     | >0.9            | 0.5             |
| High risk                                                         | 5 (3)     | 2 (1)             | 0 (0)     | 0.3             | 0.2             |
| Overall appropriate prescribing†                                  | 126 (78)  | 149 (90)          | 82 (89)   | 0.005*          | 0.045*          |
| Surgical (paediatric surgery, orthopaedics, ENT and neurosurgery) |           |                   |           |                 |                 |
| Total analysed                                                    | 118       | 69                | 108       |                 |                 |
| Optimal                                                           | 55 (47)   | 42 (61)           | 69 (64)   | 0.08            | 0.01*           |
| Adequate                                                          | 19 (16)   | 11 (16)           | 13 (12)   | >0.9            | 0.5             |
| Suboptimal                                                        | 25 (21)   | 12 (17)           | 19 (18)   | 0.7             | 0.6             |
| Inadequate                                                        | 13 (11)   | 4 (6)             | 6 (6)     | 0.3             | 0.2             |
| Unnecessary                                                       | 6 (5)     | 0 (0)             | 0 (0)     | 0.09            | 0.03*           |
| High risk                                                         | 0 (0)     | 0 (0)             | 1 (1)     | –               | 0.5             |
| Overall appropriate prescribing†                                  | 74 (63)   | 53 (77)           | 82 (76)   | 0.067           | 0.045*          |
| Total prescriptions                                               |           |                   |           |                 |                 |
| Total analysed                                                    | 348       | 359               | 323       |                 |                 |
| Optimal                                                           | 162 (47)  | 208 (58)          | 201 (62)  | 0.003*          | <0.001*         |
| Adequate                                                          | 79 (23)   | 93 (26)           | 62 (19)   | 0.4             | 0.3             |
| Suboptimal                                                        | 53 (15)   | 30 (8)            | 38 (12)   | 0.006*          | 0.2             |
| Inadequate                                                        | 31 (9)    | 16 (4)            | 21 (7)    | 0.03*           | 0.3             |
| Unnecessary                                                       | 16 (5)    | 10 (3)            | 0 (0)     | 0.2             | <0.001          |
| High risk                                                         | 7 (2)     | 2 (1)             | 1 (<1)    | 0.1             | 0.07            |
| Overall appropriate prescribing                                   | 241 (69)  | 301 (84)          | 263 (81)  | <0.001*         | <0.001*         |

\*Significant  $p < 0.05$ .

†Overall appropriate prescribing—prescription graded as optimal or adequate. app, application; ENT, ear, nose and throat.

tion in the clinical records and may not have reflected prescribers' intentions. Only empirical antimicrobial choices were investigated and other AMS features included in the Script app such as antimicrobial duration or intravenous to oral switch were out of scope. Our study design meant that we were not able to measure how often inappropriate antimicrobial prescriptions were avoided following introduction of the app. Furthermore, there was no ability to indicate the instances when the app was used in the care of individual patients in our study, so we were unable to directly

correlate prescribing with app usage. In New Zealand, there is no other similar children's hospital that could have been used as a control site to account for other temporal changes in antimicrobial prescribing. Seasonal differences in the study periods were noted with fewer skin and soft tissue infections and more respiratory infections seen in study period two which fell during winter, compared with the study period one data collected in the summer. Study period three was again in summer however, indicating that improvement was likely to be independent of seasonal variation. All Starship Clinical Guidelines which include antimicrobials are discussed with the AMS committee and many of the authors are members. This means any changes to guidance can be matched by the Script app. Script is now web based and updates to users phones every 24 hours, this means that changes can be rapidly disseminated to prescribers.

Implementation of Script for Paediatrics, a smartphone app with paediatric-specific guidelines, led to improved adherence to antimicrobial prescribing guidance in our tertiary children's hospital, as early as 4 months after the intervention and sustained after 1 year. While this intervention only evaluated changes at the national children's hospital, it is plausible that the widespread uptake of the Script app has led to improvements on a national scale. The app remains in use across the country, with regular updates, and we will continue to monitor the effect on antimicrobial prescribing. This evidence of the effectiveness of smartphone apps provides support for the implementation of similar projects in other paediatric healthcare settings.

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**Competing interests** None declared.

**Patient consent for publication** Not required.

**Ethics approval** As a quality improvement project, this was deemed out of scope for human ethics review. When accessing the app, users of the Script app consent to collection of anonymous data regarding app usage via an in-built feature of the app.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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## ARTIGO ORIGINAL

# Nem todo o vaping é igual: diferenças nos efeitos pulmonares entre canabidiol versus nicotina

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## RESUMO

**Enquadramento** — O vaping tornou-se um método popular de inalação de várias substâncias psicoativas. Embora a avaliação dos efeitos respiratórios do vaping se tenha centrado principalmente nos produtos que contêm nicotina, o vaping com canabidiol (CBD) está a tornar-se cada vez mais popular. Atualmente, desconhece-se se existe alguma semelhança entre os efeitos da nicotina e dos canabinoides na saúde.

**Objetivos** Este estudo compara, lado a lado, os efeitos pulmonares da inalação aguda de CBD vaporizado versus nicotina.

**Métodos** Foram efetuados estudos de inalação in vivo em ratos e experiências de citotoxicidade in vitro com células humanas para avaliar os efeitos indutores de danos pulmonares dos aerossóis de CBD ou nicotina emitidos pelos dispositivos de vaping.

**Medições e principais resultados** A inflamação pulmonar nos ratos foi avaliada por histologia, citometria de fluxo e quantificação dos níveis de citocinas e quimiocinas pró-inflamatórias. A lesão pulmonar foi avaliada por histologia, medição da atividade da mieloperoxidase e dos níveis de elastase de neutrófilos no líquido de lavado broncoalveolar e no tecido pulmonar. A integridade epitelial/endotelial do pulmão foi avaliada através da quantificação dos níveis de proteínas no BAL (lavado broncoalveolar), da fuga de albumina e da fuga de FITC-dextrano pulmonar. O stresse oxidativo foi determinado através da medição do potencial antioxidante no BAL e nos pulmões. Os efeitos citotóxicos dos aerossóis de CBD e nicotina nos neutrófilos humanos e nas células epiteliais das pequenas vias aéreas humanas foram avaliados utilizando o sistema de interface ar-líquido in vitro. A inalação do aerossol de CBD resultou em maiores alterações inflamatórias, danos pulmonares mais graves e maior stresse oxidativo em comparação com a nicotina. O aerossol de CBD também evidenciou uma maior toxicidade para as células humanas em comparação com a nicotina.

**Conclusões** A vaporização de CBD induz uma potente resposta inflamatória e conduz a mais alterações patológicas associadas a lesões pulmonares do que a vaporização de nicotina.

## INTRODUCTION

Electronic vaping products emerged in the late 1990s as an alternative mode of cannabis use. Cannabis vaporisers were typically large devices that heated dried cannabis herb to the point of cannabinoid vaporisation. In early 2000s, smaller portable vaporisers emerged as ‘e-cigarettes’ and have become a popular mode of nicotine administration.<sup>1</sup> E-cigarettes heat nicotine in a solution rather than from dried tobacco leaf. Recently, vaporisers in the cannabis market have followed a similar transition, with greater use of liquid cannabis extracts.<sup>2–7</sup>

Aerosols emitted from vaping products contain not only psychoactive substances like nicotine and cannabinoids (primarily tetrahydrocannabinol (THC) and cannabidiol (CBD)), but also respiratory toxicants (eg, formaldehyde, acrolein,

## Key messages

### WHAT IS ALREADY KNOWN ON THIS TOPIC

► Vaping cannabinoids using electronic devices is a growing trend, however, the pulmonary health effects of inhalation of cannabis oil are not well understood.

### WHAT THIS STUDY ADDS

► This study showed that vaping cannabinoid induces more potent inflammatory responses in the lung, greater oxidative stress and leads to augmented pathological changes associated with lung injury than vaping of nicotine.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

► This study provides insights to why potential respiratory health consequences of vaping cannabis may be more serious than those of vaping nicotine, emphasising the importance of collecting detailed information on the type of substance used by patients in their vaping products.

benzaldehyde).<sup>8–11</sup> Many chemical constituents involved in vaping nicotine and cannabinoids are similar, and others are very different, lending importance to considering these issues in the context of understanding respiratory consequences of vaping both substances. As an example, solvents used in nicotine and cannabinoid-containing vaping products can be different, due to the lipophilic properties of cannabinoids.<sup>12</sup> Vitamin E acetate was identified as an additive in THC-containing vaping products and played a significant role in the 2019 outbreak of e-cigarette and vaping-associated lung injury (EVALI).<sup>13 14</sup>

A limited number of studies on respiratory effects of vaping have primarily focused on nicotine-containing products. In vitro studies suggest that vaping nicotine can activate immune cells and impair some of their key functions.<sup>15</sup> Animal studies showed that exposure to nicotine from e-cigarettes adversely affect immunological responses.<sup>16 17</sup> Human observational studies have shown that vaping nicotine suppresses aspects of the innate immune system in nasal epithelial cells.<sup>18 19</sup> Epidemiological studies have reported associations between nicotine vaping and chronic respiratory conditions (chronic cough, bronchitis, asthma).<sup>20–24</sup> Since research on the respiratory and immunological health outcomes associated with cannabis use has exclusively focused on smoked cannabis,<sup>25–31</sup> it is currently unknown whether the

**Table 1** Comparison of chemicals detected in vaping products (unheated liquids) used in in vivo and in vitro exposure experiments

| Chemicals                        | CBD-Vape (CalmVape from The Kind Group)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Nic-Vape (Juul by Juul Labs)                                                                                                                                                                                                                                                                          |
|----------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| CBD                              | 43.9 mg/mL                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Not detected                                                                                                                                                                                                                                                                                          |
| $\Delta$ -9 Tetrahydrocannabinol | Not detected                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Not detected                                                                                                                                                                                                                                                                                          |
| Nicotine                         | Not detected                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 48.9 mg/mL                                                                                                                                                                                                                                                                                            |
| Solvent                          | MCT (medium chain triglycerides) – mixture of caprylic acid (C8), capric acid (C10), and lauric acid (C12)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Mixture of propylene glycol and vegetable glycerin                                                                                                                                                                                                                                                    |
| Flavourings and terpenes         | Amylene hydrate ( <i>pungent</i> ); Benzyl alcohol ( <i>chemical, fruity cherry, almond, balsamic, bitter</i> ); Carvone ( <i>sweet, minty, spearmint, carvone, caraway</i> ); Linalol ( <i>citrus, orange, lemon, floral, waxy, aldehydic, woody</i> ); Caryophyllene ( <i>spicy, clove, woody, nut skin, powdery, peppery</i> ); Octanoic acid ( <i>rancid, soapy, cheesy, fatty, brandy</i> ); Decanoic acid, methyl ester ( <i>fatty, oily, fruity</i> ); Octanoic acid, methyl ester ( <i>green, fruity, waxy, citrus, aldehydic and fatty</i> ); Caryophyllene oxide ( <i>dry, woody, cedar, old wood, carrot, ambrette</i> ); Cherry propanol ( <i>fruity, cherry, sweet, hay-like with cereal and bread like nuances</i> ); Cis-carveol ( <i>caraway</i> ); Ethanone, 1-(4-methylphenyl)- ( <i>sweet, creamy, fruity, cherry and heliotropine-like</i> ) | Amylene hydrate ( <i>pungent</i> ); 2-Propanol, 1,1'-oxybis- ( <i>alcoholic</i> ); Benzaldehyde, 3,4-dimethoxy- ( <i>sweet, creamy, vanilla</i> ); Azolidine ( <i>fishy</i> ); Triethyl citrate ( <i>mild fruity wine</i> ); Butyrolactone ( <i>milky, creamy with fruity peach like afternotes</i> ) |
| Other additives                  | Not detected                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Benzoic acid (combines with nicotine to create nicotine salt ( <i>nicotine benzoate</i> ))                                                                                                                                                                                                            |

CBD, cannabidiol; MCT, medium chain triglycerides.

health effects of vaping nicotine and cannabinoids are similar. This study aimed to compare, in a side-by-side format, the impact of acute inhalation of vaporised cannabinoid versus nicotine.

## MATERIALS AND METHODS

Methods used are described in greater detail in online supplemental file.

### Vaping products

We used two commercial vaping products, one containing CBD and the other containing nicotine (abbreviated in figures as CBD-vape and Nic-vape). The CBD-containing pod was Calm-Vape from The Kind Group LLC and the nicotine-containing pod was Juul by Juul Labs. Both products were purchased online in USA in November 2020. CalmVape pods were labelled as containing 50 mg/mL of CBD dissolved in a mixture of medium chain triglycerides (MCT) and had natural flavour. Juul was labelled as containing 5.0% nicotine dissolved in a mixture of propylene glycol (PG) and vegetable glycerin (VG) and Virginia Tobacco flavour. We tested unheated and heated liquids as well as emissions generated from both products using fully-validated and previously published chromatography–mass spectrometry assays.<sup>32</sup> Primary ingredients identified in the liquids from the two products are listed in table 1. Detailed list of chemicals identified in heated solutions, including yields of four potentially toxic carbonyl compounds (formaldehyde, acetaldehyde, acetone and acrolein) in emitted aerosols are provided in online supplemental figures E1–E4 and online supplemental tables E1 and E2.

### Mice

Six-week-old C57BL/6NCR male and female mice were procured from Charles River Laboratory (Wilmington, Massachusetts, USA) and housed under specific pathogen-free conditions with light/dark cycle of 12/12 hours. The number of animals per exposure group was n=10 (5 males and 5 females, except for Nic-vape which contained 5 males and 4 females; one female mouse was very small in size and needed to be euthanised before study completion). All experiments were performed in accordance with the guidelines established by the Institutional Animal Care and Use Committee and complied with all state, federal and NIH regulations.

### Animal exposure conditions

Aerosols from vaping products were produced using an e-cigarette aerosol generator described previously.<sup>14 33</sup> The Juul device was used to aerosolize both the products. Animals were exposed in a modified 15 L induction chamber each day to a total of 20 puffs generated over 1 hour (1 puff every 3 min), 5 days/week for 2 weeks. Each puff had a volume of 55 mL and was aerosolized over 3 s duration. Aerosols from each vaping product were generated using identical puffing protocol intended to mimic vaping

behaviour of experienced nicotine vapers.<sup>34</sup> Due to lack of publications describing vaping behaviour among CBD vapers, we followed the same puffing protocols for both products. Although we did not measure airborne CBD and nicotine inside animal exposure chambers, we have estimated based on volume of liquid vaporised per day, CBD and nicotine concentration in liquids, aerosol and air flow rates that animals were exposed on average to 20.5 mg/m<sup>3</sup> CBD and 22.8 mg/m<sup>3</sup> nicotine. Control animals were exposed to filtered air using the same exposure protocol.

### In vitro exposure conditions

Cells used in in vitro experiments were directly exposed to freshly generated puffs in a closed exposure system where air–liquid interface (ALI) chambers were kept inside a 37°C incubator. For ALI experiments, we used the same closed-system vaping devices and refill liquid formulations as used for in vivo exposure experiments described above. Details of the method are provided in online supplemental file.

### Assessment of pulmonary inflammation

Pulmonary inflammation was scored by flow cytometry, histochemistry, and by quantifying levels of cytokines and chemokines (online supplemental figure E5)<sup>14 35 36</sup> and complete details are provided in online supplemental file.

### Assessment of lung damage

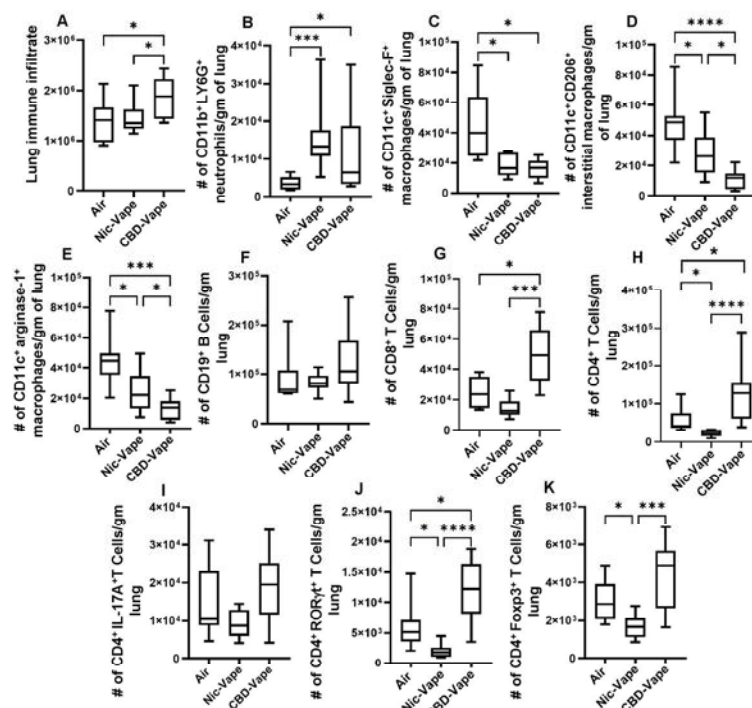
Lung epithelial/endothelial integrity was assessed by quantifying protein levels by BCA, and systemic to bronchoalveolar space albumin leak by ELISA using BAL samples and bronchoalveolar to systemic leak by measuring plasma fluorescence 1 hour after intratracheal instillation of fluorescent probe. Neutrophil elastase (NE) levels,<sup>37 38</sup> were measured in BAL and lung tissue using a NE ELISA kit from R&D systems (Cat. #DY4517-05) following manufacturer's protocol. Myeloperoxidase activity (MPO) was measured by calorimetric assay in the BAL and lung tissue<sup>39</sup> using MPO assay kit from Abcam (Cat. #ab105136) using manufacturer's instructions. Oil Red O stain was used to visualise lipid-laden alveolar macrophages.<sup>14</sup> Assay details are given in online supplemental file. Histological evaluations in sections of lungs were graded by a veterinary pathologist as described previously.<sup>40 41</sup>

### Measurement of oxidative stress in mice BAL and lungs

Acute inflammatory responses rapidly overwhelm antioxidant systems to promote lung injury.<sup>42–44</sup> Oxidative stress was determined by measuring the antioxidant potential in the BAL and lung lysates as described in online supplemental file.

### In vitro cytotoxicity tests

Human small airway epithelial cells (hSAECs) from LONZA and purified human neutrophils were directly exposed to freshly gen-



**Figure 1** Impact of acute exposure to CBD or nicotine aerosols on pulmonary immune-cell infiltration. Total number of leucocytes (A), CD11b<sup>+</sup>Ly6G<sup>+</sup> neutrophils (B), CD11b<sup>+</sup>CD11c<sup>+</sup>Siglec-F<sup>+</sup> macrophages (C), CD11b<sup>+</sup>CD11c<sup>+</sup>CD206<sup>+</sup> macrophages (D), CD11b<sup>+</sup>CD11c<sup>+</sup>arginase<sup>+</sup> macrophages (E) and numbers of CD19<sup>+</sup> B cells (F), CD8<sup>+</sup> T cells (G), CD4<sup>+</sup> T cells (H), CD4<sup>+</sup>IL17A<sup>+</sup> (I) and CD4<sup>+</sup>RORγt<sup>+</sup> inflammatory T cells (J) and CD4<sup>+</sup>FOXP3<sup>+</sup> T cells (K) in the lungs of mice exposed to air, nicotine, or CBD aerosol were determined by flow cytometry using specific markers and following a gating strategy as described previously and shown in online supplemental figure 1. Data are shown as box plots with whiskers at min and max. Difference between two groups is considered significant at  $p < 0.05$ , statistical significance of the difference between two groups is indicated with symbols \* $p < 0.05$ ; \*\*\* $p < 0.001$ ; \*\*\*\* $p < 0.0001$  after performing non-parametric Kruskal-Wallis test with false discovery rate (FDR) correction for multiple comparisons by GraphPad Prism V.9 software (GraphPad; La Jolla, California, USA). In each exposure condition,  $n = 10$  mice (5 males+5 females) for Nic-Vape) were used. CBD, cannabidiol.

erated CBD and nicotine aerosols in air-liquid interface cultures. Exposure protocol and methodological details are in online supplemental material. Cytotoxicity was measured using trypan blue-dye exclusion, neutral red dye uptake and Annexin V-FITC apoptosis assays as described in online supplemental file.

#### Measurement of NE levels in PMN culture media

NE levels in the aerosol-exposed PMN cell culture conditioned media after recovery period were quantified by ELISA kit from R&D systems (Cat. #DY4517-05) following manufacturer's instructions.

#### FITC-dextran permeability assay

Paracellular permeability, across a monolayer of aerosol-exposed human SAECs from ALI cultures, was performed to assess barrier integrity and details are described in online supplemental file.

#### Statistical analysis

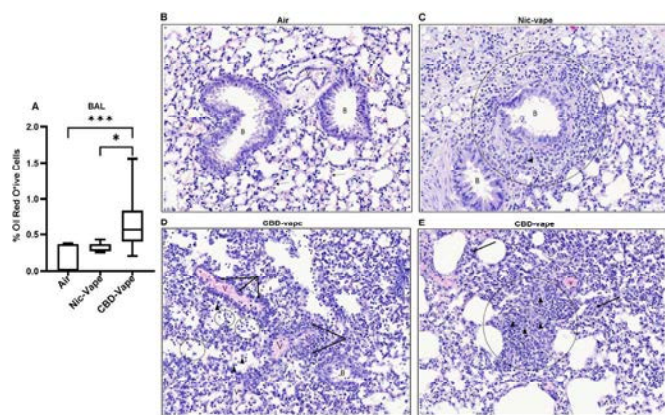
Statistically significant differences between the mean rank values of different exposure groups (CBD, nicotine and air controls) were determined by performing Kruskal-Wallis's non-parametric test. P values were corrected for multiple testing using the 'two-stage linear step-up procedure of Benjamini, Krieger and Yekutieli' false discovery rate (FDR) method and the differences between two groups were considered statistically significant at  $p < 0.05$  when FDR was set at  $Q < 0.1$ . We also evaluated if there were differences between male versus female mice in the responses to inhalation of CBD and nicotine aerosols in comparison with air. All statistical analyses were carried out using GraphPad Prism V.9.3.1 software (GraphPad; La Jolla, California, USA).

## RESULTS

### Exposure to CBD aerosol resulted in greater accumulation of innate and adaptive immune cells in lungs compared with nicotine exposure

Total immune cell infiltrate was significantly higher in the lungs of mice following inhalation of CBD aerosols than nicotine or

filtered air (figure 1A). Seven of the 10 subsets of immune cells studied were significantly more impacted following CBD exposure compared with nicotine. Immunophenotypic analysis revealed a statistically significant infiltration of CD11b<sup>+</sup>Ly6G<sup>+</sup> neutrophils in the lungs of mice following inhalation of CBD-aerosols (14 488 vs 3674 neutrophils in air,  $p < 0.05$ ) as well as following nicotine aerosol-exposure (15 410 vs 3674 neutrophils in air,  $p < 0.001$ ) (figure 1B). Total numbers of CD11b-CD11c<sup>+</sup>Siglec-F<sup>+</sup> alveolar macrophages were significantly reduced following CBD-Vape or Nic-Vape inhalation as compared with air exposed mice (15 965 cells in CBD and 18 834 cells in Nic-Vape vs 43 465 cells in air ( $p < 0.05$ )) (figure 1C). Inhalation of both CBD and nicotine aerosols resulted in significantly lower numbers of pulmonary interstitial CD11b-CD11c<sup>+</sup>CD206<sup>+</sup> macrophages as compared with air-exposed control mice (11 460 vs 47 319 cells for CBD-Vape,  $p < 0.0001$ ) and 27 727 vs 47 319 cells for Nic-Vape,  $p < 0.05$ ). The reduction in the numbers of pulmonary interstitial macrophages was significantly greater following inhalation of CBD aerosols compared with nicotine (11 460 cells in CBD-vape vs 27 727 cells in Nic-Vape,  $p < 0.05$ ) (figure 1D). CD11b-CD11c<sup>+</sup>arginase-1<sup>+</sup> macrophages were significantly reduced following inhalation of both CBD-Vape and Nic-Vape compared with air-exposed control (13 450 vs 44 009 for CBD-Vape ( $p < 0.001$ ), and 24 280 vs 44 009 for Nic-Vape ( $p < 0.05$ )) (figure 1E). However, the reduction in the numbers of CD11b-CD11c<sup>+</sup>arginase-1<sup>+</sup> macrophages was significantly more following inhalation of CBD aerosols compared with Nic-Vape (13 450 cells in CBD-vape vs 24 280 cells in Nic-Vape ( $p < 0.05$ )). The number of CD19<sup>+</sup> B cells were not statistically different (figure 1F). Following inhalation of CBD aerosols, the numbers of CD8<sup>+</sup> and CD4<sup>+</sup> T cells in the lungs were, respectively, 3.3-fold ( $p < 0.001$ ) and 5.6-fold ( $p < 0.0001$ ) higher than following nicotine inhalation (figure 1G,H). CD4<sup>+</sup>IL-17A<sup>+</sup> T cells were not altered in the lungs following CBD-Vape or Nic-Vape exposures as compared with air control (figure 1I). CD4<sup>+</sup>RORγt<sup>+</sup> T cells, expressing the master transcription factor essential for the differentiation into proinflammatory Th17 cells, were significantly

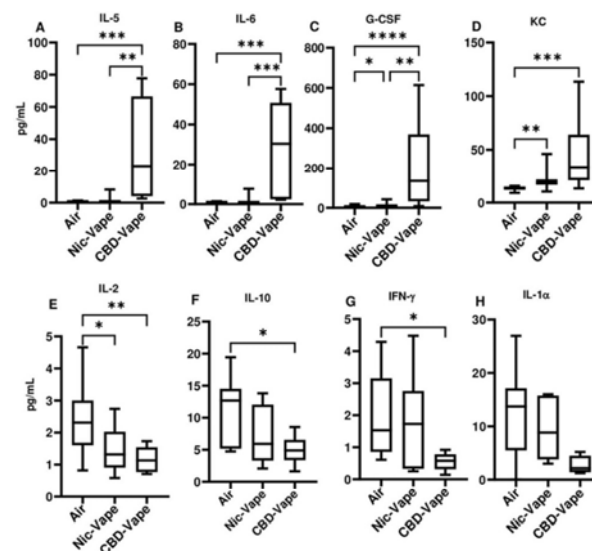


**Figure 2** Inflammatory changes in the lungs following inhalation exposure to CBD and nicotine aerosols. At the end of the exposures, mice were euthanised, trachea cannulated to collect BAL in 1% FBS in PBS and lungs harvested. (A) BAL cells cyto-spun on glass slides were stained with 0.5% Oil Red O solution and Oil Red O-positive cells were counted as described in methods. Results are depicted as box plots with whiskers at min and max. Difference between two groups is considered significant at  $p < 0.05$  and indicated with the symbols \* $p < 0.05$ ; \*\*\* $p < 0.001$  by performing non-parametric Kruskal-Wallis test with FDR correction for multiple comparisons using GraphPad Prism V.9 software (GraphPad; La Jolla, California, USA). In each experiment  $n = 10$  (5 males+5 females) for CBD-vape and air exposure and  $n = 9$  (5 males+4 females) for Nic-vape. (B–E) Left lung lobes from all mice were embedded, sectioned and H&E stained as described in methods. (B) (Air): Image of histologically unremarkable lung from air-breathing control mouse showing air-filled alveolar lumina bounded by thin alveolar walls (arrows). H&E,  $\times 20$ . (C) Nic-vape: Peribronchiolar lymphocytic, macrophagic (arrowhead) granulocytic infiltrate (circle). H&E,  $\times 20$  magnification. B=bronchiolar lumen. (D, E) CBD-vape: Perivascular infiltrates composed of mononuclear (lymphocytes and macrophages) and granulocytic infiltrates (arrows). Intra-alveolar granulocytes (circles) and macrophages (arrowheads) were also present. H&E,  $\times 20$  magnification. BD, cannabidiol; B, bronchiolar lumen; FDR, false discovery rate; PBS, phosphate-buffered saline; V, vessel lumen.

increased following inhalation of CBD aerosols as compared with both nicotine (11 983 vs 2015;  $p < 0.001$ ) and air-exposure (11 983 vs 5887;  $p < 0.05$ ) (figure 1J). Furthermore, CBD aerosols resulted in markedly increased infiltration of CD4<sup>+</sup>Foxp3<sup>+</sup> regulatory T cells into the lungs compared with nicotine (4401 cells in CBD-Vape vs 1688 cells in Nic-Vape;  $p < 0.001$ ) (figure 1K). There were no statistically significant differences observed between male and female mice concerning the infiltration of any of the innate and adaptive immune cells, regardless of the different exposure conditions (online supplemental figure E6A–K).

Relatively more Oil Red O-positive lipid-laden macrophages were detected in BAL following CBD-aerosol inhalation compared with nicotine aerosol (0.66 vs 0.32;  $p < 0.05$ ) or air-exposure (0.66 vs 0.15;  $p < 0.001$ ) (figure 2A). Lung tissue sections of air-breathing mice contained rare (typically 1–2 positive cells in entire lung lobe) lipid-containing, Oil Red O-positive intra-alveolar macrophages (online supplemental figure E7A). In contrast, lungs from CBD and nicotine exposed animals regionally contained one or more Oil Red O-positive macrophages within multiple alveolar lumina that were often adjacent to one another (online supplemental figure E7B,C), with no obvious differences found in males versus females.

Histological examination of H&E-stained lung tissue sections from filtered air breathing control mice showed air-filled alveolar lumina bounded by thin alveolar walls (figure 2B). In contrast, peribronchiolar and/or intrabronchiolar, perivascular, alveolar infiltrates and interstitial infiltrates of lymphocytes, macrophages and granulocytes were the predominant finding in the CBD and nicotine exposed mouse lungs (figure 2C–E). Small focal lesions and occasionally larger and more regionally extensive focal



**Figure 3** Modulation of the inflammatory cytokine/chemokine milieu in the BAL fluid following inhalation of CBD and nicotine aerosols. Levels of various inflammation-related cytokines and chemokines in the BAL (A–H) of mice after 2 weeks of exposure to air, Nic-Vape aerosols or CBD-Vape aerosols were quantified using MILLIPLEX MAP Kit as described in materials and methods. Data are shown as box plots with whiskers at min and max. Non-parametric Kruskal-Wallis test with FDR correction for multiple comparison was performed to see if statistically significant differences exist between two groups using GraphPad Prism V.9 software (GraphPad; La Jolla, California, USA). Difference between two groups is considered significant at  $p < 0.05$  and are indicated with symbols \* $p < 0.05$ ; \*\* $p < 0.01$ ; \*\*\* $p < 0.001$ ; \*\*\*\* $p < 0.0001$ . In each experiment  $n = 10$  for CBD-vape and air exposure (5 males+5 females) and  $n = 9$  (5 males+4 females) for Nic-Vape. CBD, cannabidiol.

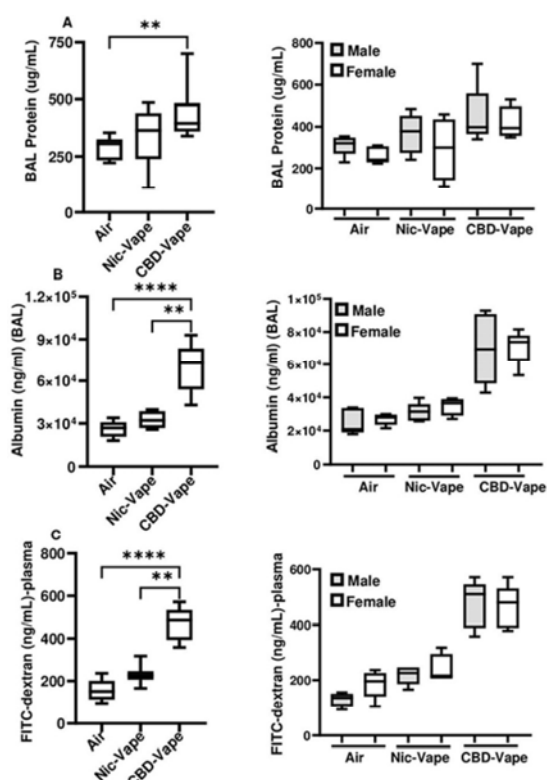
lesions were noted. Lesions were found primarily near terminal bronchioles and often subpleural. The frequency and severity of lesions was greater following CBD aerosol inhalation compared with nicotine. The male mice showed a greater frequency of most lesions as compared with female mice following inhalation of both CBD and nicotine.

### CBD aerosol had a stronger modulatory effect on cytokine levels than nicotine aerosol

We found that CBD aerosol-inhalation significantly augmented the levels of cytokines IL-5, IL-6 and G-CSF in the BAL compared with both nicotine and air exposures ( $p < 0.01$ ) and significantly enhanced the levels of chemokine KC compared with air-control only ( $p < 0.001$ ) (figure 3A–D). Levels of IL-2 were significantly lower following CBD and Nic-vape aerosol-exposures compared with air ( $p < 0.05$ ) (figure 3E). IL-10 and IFN- $\gamma$  levels were significantly reduced only after CBD aerosol-exposure compared with air ( $p < 0.05$ ) (figure 3F,G). IL-1 $\alpha$  levels were not significantly different, though there was a trend for the values to be lower following exposure to CBD-Vape aerosols (figure 3H). There were no statistically significant differences observed between male and female mice in the levels of these cytokines or chemokines (online supplemental figure E8A–H and online supplemental table E3).

### Exposure to CBD aerosols resulted in more lung endothelial damage than exposure to nicotine aerosol

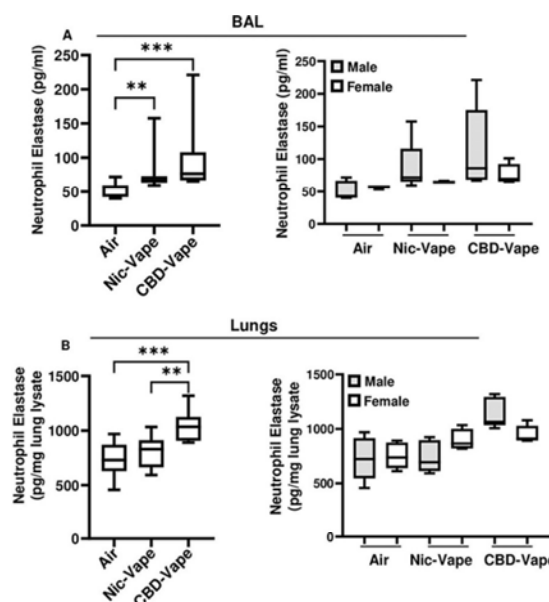
Total protein levels in the BAL were elevated following the inhalation of CBD aerosols when compared with air controls (435  $\mu\text{g/mL}$  vs 287  $\mu\text{g/mL}$ ;  $p < 0.01$ ) (figure 4A, left panel). Additionally, serum albumin levels leaking into the BAL were markedly increased



**Figure 4** Markers of lung damage induced after inhalation exposure to CBD and nicotine aerosols. At the end of the exposures, mice were euthanised, BAL harvested and the levels of (A) total proteins and (B) albumin in the BAL were quantified as described in the Materials and Methods section. (C) Levels of FITC-dextran leaking into plasma were quantified. Left panels in each figure represent data from Males+Females combined, while right panels represent data as male versus females. Results are shown as box plots with whiskers at min and max. Differences between groups is considered significant at  $p<0.05$  and are indicated as symbols \*\* $p<0.01$ , \*\*\*\* $p<0.0001$ , calculated after performing non-parametric Kruskal-Wallis test with FDR correction for multiple comparisons by employing GraphPad Prism V.9 software (GraphPad; La Jolla, California, USA). In each experiment  $n=10$  (5 males+5 females) for air and CBD-vape exposures and  $n=9$  (5 males+4 females) for Nic-Vape group. CBD, cannabidiol.

following CBD aerosol inhalation when compared with both nicotine aerosol (70 303 ng/mL vs 32 741 ng/mL in Nic-Vape;  $p<0.01$ ) and air inhalation (70 303 ng/mL vs 26 042 ng/mL in air control;  $p<0.0001$ ) (figure 4B, left panel). Systemic leak of FITC-dextran from the lungs into the plasma was markedly higher following CBD aerosol inhalation than Nic-vape aerosol (469.9 ng/mL vs 227.6 ng/mL in Nic-Vape;  $p<0.01$ ) or air exposures (469.9 ng/mL vs 157.5 ng/mL in air control;  $p<0.0001$ ) (figure 4C, left panel). Furthermore, FITC-dextran leak following Nic-vape aerosol exposure was not significantly different when compared with air control (227.6 ng/mL vs 157.5 ng/mL). There were no statistically significant differences observed in the levels of these markers when comparing male with female mice following any of the exposures (figure 4A–C, right panels and online supplemental table E3).

It is known that elastase activity in inflammatory diseases increases and correlates with the levels of elastase proteins and neutrophil infiltrates as the disease progresses.<sup>45,46</sup> NE levels in the BAL were markedly augmented following inhalation of CBD aerosols (1.8-fold vs air;  $p<0.001$ ) and Nic-Vape aerosols (1.42-fold vs air;  $p<0.01$ ) (figure 5A, left panel). The levels of NE measured in lung tissue were significantly increased following CBD-Vape as compared with both Nic-Vape (1.3-fold;  $p<0.01$ ) and air (1.41-fold;  $p<0.001$ ) (figure 5B, left panel). There were no statistically significant differences observed in NE levels between male and female mice, measured either in the BAL or lung tissues (figure 5A,B, right panels and online supplemental table E3).



**Figure 5** Levels of neutrophil elastase in lungs measured after exposure to CBD and nicotine aerosols. At the end of the 2-week exposures, mice were euthanised, BAL and lungs harvested, and tissue lysates prepared. (A, B) NE levels in the BAL and lung tissue lysates were quantified by ELISA. Left panels in each figure show data as males+females combined, while right panels represent data as male versus Females. Results are shown as box plots with whiskers at min and max. Non-parametric Kruskal-Wallis test with FDR correction for multiple comparisons was used to see if statistically significant differences exist between two groups using GraphPad Prism V.9 software (GraphPad; La Jolla, California, USA). Difference between two groups was considered significant at  $p<0.05$  and are indicated with symbols \*\* $p<0.01$ , \*\*\* $p<0.001$ . In each experiment  $n=10$  (5 males+5 females) for air and CBD-vape exposures each and  $n=9$  (5 males+4 females) for Nic-Vape. CBD, cannabidiol; NE, neutrophil elastase.

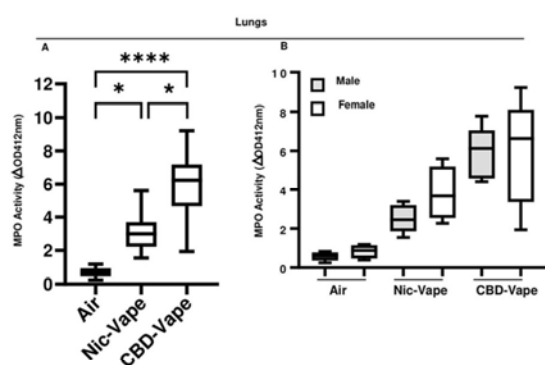
We detected higher MPO activity in lung tissues following inhalation of CBD aerosols compared with nicotine aerosols (~2 fold;  $p<0.05$ ) and air (~8.44 fold;  $p<0.0001$ ) (figure 6A). BAL MPO activity following CBD and nicotine aerosol-inhalation was equivalent, but greater than air controls ( $p<0.01$ ) (online supplemental figure E9A). There were no statistically significant differences observed in MPO activity between male and female mice, either in lung tissue or in the BAL (figure 6B; online supplemental figure E9B and online supplemental table E3).

#### Exposure to CBD and nicotine aerosols decreased pulmonary antioxidant potential

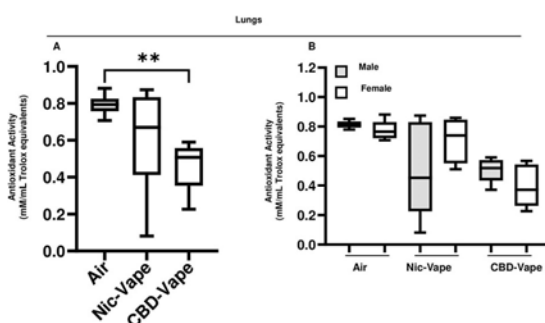
The total antioxidant capacity was markedly decreased in both lung tissue ( $p<0.01$  vs air) and BAL ( $p=0.001$  vs air) following inhalation of CBD aerosols (figure 7A; online supplemental figure E10A). However, following nicotine aerosol-exposure it was significantly reduced only in the BAL ( $p<0.01$  vs air) compared with air (online supplemental figure E10A). We did not observe any statistically significant differences in the antioxidant potential between male and female mice for each exposure group, either in lung tissue or in the BAL (figure 7B; online supplemental figure E10B and online supplemental table E3).

#### CBD aerosol was more toxic than nicotine aerosol to hSAECs and disrupted their epithelial barrier integrity

We observed that when human SAECs were exposed in vitro to CBD aerosols for 1 hour, epithelial cell morphology was markedly

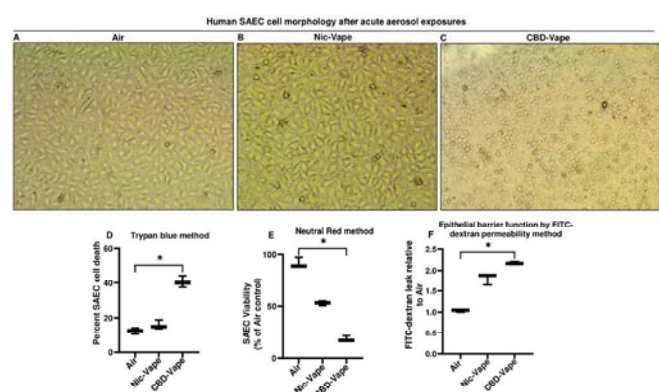


**Figure 6** Augmentation of the myeloperoxidase (MPO) activity in lungs after exposure to CBD and nicotine aerosols. (A, B) We measured MPO activity in lung tissue lysates of nicotine or CBD aerosol-exposed animals using MPO assay kit from Abcam as described in detail in the supplemental material section. Left panel depicts data as males+females, while right panel represents data as male versus females. Data shown as box plots with whiskers at min and max. Non-parametric Kruskal-Wallis test with FDR correction for multiple comparisons was performed to see if statistically significant differences exist between two groups using GraphPad Prism V.9 software (GraphPad; La Jolla, California, USA). Difference between two groups was considered significant at  $p < 0.05$  and is indicated with the symbols \* $p < 0.05$ , \*\*\*\* $p < 0.0001$ . In each experiment  $n = 10$  mice for air and CBD-vape exposures each (5 males+5 females) and  $n = 9$  for Nic-Vape group (5 males+4 females). CBD, cannabidiol; FDR, false discovery rate.



**Figure 7** Changes in antioxidant potential in the lung following exposure to CBD and nicotine aerosols. At the end of the exposures to nicotine or CBD aerosols, mice were euthanised and lung tissue lysates were prepared. (A, B) Total antioxidant levels in lung tissue lysates were quantified using Cayman's antioxidant assay kit (Cat# 709001) as described in detail in online supplemental material section. Left panel depicts data as males+females combined, while right panel represents data as male versus females. Data shown as box plots with whiskers at min and max. Non-parametric Kruskal-Wallis test with FDR correction for multiple comparisons was used to see if statistically significant differences exist between two groups using GraphPad Prism V.9 software (GraphPad; La Jolla, California, USA). Difference between two groups was considered significant at  $p < 0.05$  and is indicated with the symbol \*\* $p < 0.01$ . In each experiment,  $n = 10$  mice for air and CBD-vape exposures each (5 males+5 females) and  $n = 9$  for Nic-Vape group (5 males+4 females). CBD, cannabidiol; FDR, false discovery rate.

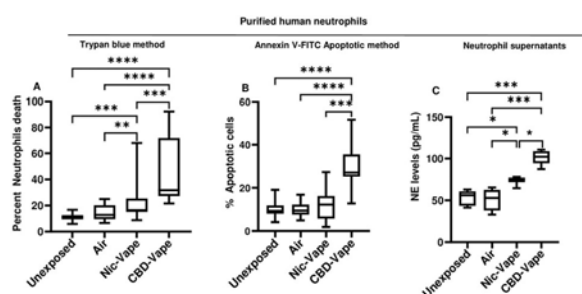
disrupted (figure 8A,B vs 8C). Cell death in hSAECs was significantly increased only following CBD aerosol-exposure when compared with air (41% vs 12.5% in air control;  $p < 0.05$ ) (figure 8D,E). Even though the cell death following CBD-Vape exposure was higher compared with exposure to nicotine aerosols, it, however, did not reach statistical significance (41% vs 16% in Nic-Vape). Additionally, exposure to CBD aerosols diminished the epithelial barrier integrity of human SAECs compared with air by 2.1-fold ( $p < 0.05$ ) and while the exposure to nicotine aerosols also showed an increased trend, it was not significantly different compared with air-control (1.7-fold decrease in Nic-Vape vs air control) (figure 8F).



**Figure 8** Epithelial cell morphology, cytotoxicity and epithelial barrier integrity of human small airway epithelial cells (SAEC) following exposure to CBD and nicotine aerosols. Human SAECs (0.5 million cells/culture insert in a 6-well plate format) were cultured in complete growth media overnight and next day directly exposed at the air-liquid interface (ALI) to 110 puffs of air, nicotine (50 mg/mL nicotine) or CBD (50 mg/mL)-containing aerosols as described in methods. All aerosols were generated in a 55 mL puff volume as described in the Methods section. At the end of the exposures, cells were removed from the ALI chamber and incubated in complete growth media for 24 hours at 37°C. After recovery period ended, cells were first imaged (A–C) at  $\times 200$  in a phase-contrast microscope (Olympus IX73) and then cell toxicity assays using (D) trypan blue method (measured as percent cell death) or (E) neutral red uptake method (depicted as percent of air control) were performed. For (F) FITC-dextran permeability assay, 1 million human SAECs/culture insert were cultured overnight and next day directly exposed at the ALI to 110 puffs of air, nicotine (50 mg/mL nicotine) or CBD (50 mg/mL)-containing aerosols. On completion of the exposures, FITC-dextran at 10 mg/mL concentration was added to the apical chamber and incubated for 2.5 hours. Samples were harvested from the basolateral chamber and fluorescence measured using Exci485/Emi528 wavelengths in a synergy H1 hybrid plate reader (BioTek). The concentration of FITC-dextran in the basolateral chamber was calculated using a standard curve. Difference between two groups was considered significant at  $p < 0.05$  and is indicated with the symbol \* $p < 0.05$ , calculated using non-parametric Kruskal-Wallis test with FDR correction for multiple comparisons by GraphPad prism V.9 software (GraphPad; La Jolla, California, USA). Results are depicted as box plots with whiskers at min and max from three independent experiments each performed in triplicate as described in online supplemental methods. CBD, cannabidiol; FDR, false discovery rate; SAECs, small airway epithelial cells.

### CBD aerosols but not nicotine aerosols induced apoptotic cell death in purified human neutrophils, but both enhanced the release of NE

Acute exposure to CBD aerosols induced marked cell death in purified human neutrophils (44.5% cell death following CBD-Vape vs 14% in air control;  $p < 0.0001$ ) and (44.5% vs 21% cell death in Nic-Vape;  $p < 0.001$ ) (figure 9A). CBD aerosol-induced neutrophil cell death was mainly due to increased apoptosis compared with air (29% vs 10% in air control;  $p < 0.0001$ ) and compared with Nic-Vape (29% vs 12% in Nic-Vape;  $p < 0.001$ ) (figure 9B). Furthermore, both CBD and nicotine aerosols lead to enhanced accumulation of NE levels in the neutrophil cell culture media as compared with air control (2-fold increase in CBD-Vape;  $p < 0.001$  and 1.45-fold increase in Nic-Vape;  $p < 0.05$ ) (figure 9C). However, the levels were significantly higher following CBD versus nicotine exposure (CBD-Vape 1.4-fold higher than Nic-Vape;  $p < 0.05$ ) (figure 9C). Pictures of human neutrophils after ALI exposures and 24-hour recovery period are provided in online supplemental figure E12. Importantly, an aliquot of purified neutrophils that were incubated in media (unexposed) for the duration of the experiment showed low cell death (~11%) that was equivalent to values noted in neutrophils exposed to air (~14%) in the ALI chambers (figure 9A), nor was apoptosis or increased NE levels induced (figure 9B,C).



**Figure 9** Apoptotic cell death in purified human neutrophils and levels of neutrophil elastase (NE) released after exposure to CBD and nicotine aerosols. Human neutrophils purified from whole blood were seeded at 0.8 million cells/culture insert in a 6-well plate format and immediately exposed to 110 puffs of Air, nicotine (50 mg/mL nicotine) or CBD (50 mg/mL)-containing aerosols at the air-liquid interface in a 55 mL puff volume as described in the Methods section. At the end of the exposures, cells were removed from the ALI chamber and recovered in complete growth media for 24 hours. Next, cell death was measured using (A) trypan blue dye-exclusion assay and (B) annexin V-FITC apoptosis as mentioned in detail in the Methods section. Immediately after isolation, an aliquot of the purified neutrophils was kept in complete medium in a CO<sub>2</sub> incubator as negative 'unexposed controls' for the entire duration of the assay, to estimate the extent of cell death, induction of apoptosis, or NE levels in the absence of any exposure. (C) Levels of NE were quantified in conditioned media harvested after recovery period ended by performing NE ELISA as discussed in the Methods section. Data are depicted as box plots with whiskers at min and max from independent experiments each performed in triplicate. For apoptosis assay: average data from n=5 donors per group. For trypan blue method: average data from unexposed control n=6 donors, air control and Nic-Vape n=7 donors, and CBD-Vape n=8 donors. For NE assay average data from n=6 donors per group. Difference between two groups was considered significant at  $p < 0.05$  which is indicated with the symbols \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$ , \*\*\*\* $p < 0.0001$  calculated using non-parametric Kruskal-Wallis test with FDR correction for multiple comparisons by GraphPad Prism V.9 software (GraphPad; La Jolla, California, USA). ALI, air-liquid interface; CBD, cannabidiol; FDR, false discovery rate.

## DISCUSSION

Our findings revealed that detrimental effects on immune system and lung damage after inhalation exposure to cannabinoid-containing vaping product were more severe than after exposure to aerosols from a nicotine-containing vaping device. We have uncovered the harmful effect of vaporised CBD impacting pulmonary immune homeostasis using a mouse model of vaping and in vitro experiments with human cells. Our studies revealed that CBD vaping induces a proinflammatory pulmonary microenvironment, leading to marked accumulation of inflammatory immune cells exhibiting enhanced activity of tissue-damaging factors like MPO and NE and leading to induction of lung injury via processes that might include oxidative stress.

Although several studies have examined the respiratory effects of vaping nicotine, to our knowledge, this is the first report that demonstrates that even short-term exposure to vaporised CBD alters the inflammatory milieu in the lung, leading to lung damage. It is important to note that we used CBD-containing vaping products devoid of THC, to eliminate any potential influence of THC on pulmonary effects. Due to legal restrictions in accessing vaping products containing THC, we were unable to conduct experiments that would also compare the effects of THC vaping. A single recent study reported that CBD in vaping products can be considered as a precursor of THC, thus compounding the problem further by inducing CBD-independent, THC-mediated effects related to general use of cannabis vaping products.<sup>47</sup> Furthermore, suggesting that both products are susceptible to high temperatures. However, higher levels of carbonyl compounds were detected in CBD-containing aerosol, suggesting that CBD vaping product used in our study may have been more susceptible to thermal degradation compared with nicotine product. This may be due to differences

in chemical composition of two solutions and/or differences in vapourisation conditions inside vaping devices.

Numerous markers of inflammation and pulmonary damage measured in our study were consistently higher after exposure to CBD-containing vaping product than nicotine-containing vaping device. For example, we report that inhalation of aerosolized CBD vape oil caused a much stronger enhancement in the numbers of both CD4<sup>+</sup> and CD8<sup>+</sup> T cells, and high numbers of neutrophils in the lungs. A similar profile of increased neutrophils and modulation of CD4<sup>+</sup> and CD8<sup>+</sup> T cells was seen in the lung of a patient who had vaped cannabis oil causing lung injury and respiratory failure.<sup>3</sup> A tight nexus exists between inflammatory T cells, neutrophil-mobilising factors and neutrophil recruitment in pulmonary inflammatory disorders.<sup>48</sup> An increased inflammatory milieu in the lungs after exposure to CBD aerosols could orchestrate accumulation and/or activation of neutrophils in the bronchoalveolar space directly, via release of specific neutrophil-mobilising factors like IL-6, G-CSF and KC (CXCL1) or indirectly via activation of resident lung macrophages and epithelial cells.<sup>49,50</sup> It is also possible that CBD aerosols could damage lung epithelium and initiate a process of neutrophil recruitment and activation via mechanisms including local tissue damage.<sup>51</sup> Indeed, we demonstrate that CBD aerosols damage epithelial integrity and induce cell death in hSAECs, suggesting that CBD aerosols could directly induce lung-tissue damage and activate DAMPs to mediate pulmonary inflammation.

Neutrophil infiltration and NE-induced lung-tissue destruction is known to mediate cigarette smoke-induced pulmonary damage and compromised epithelial barrier integrity.<sup>52–56</sup> Neutrophils after homing to the lung exhibit an activated phenotype and perpetuate the inflammatory process,<sup>57</sup> so we reasoned that augmentation of the numbers of neutrophils accumulating in the lungs of mice exposed to CBD aerosols (14 488 vs 3674 in air) might have biological consequences due to their activation status. These granulocytic cells are the source of two important factors, myeloperoxidase and NE that are involved in microbicidal activity and pulmonary remodelling. The enhanced levels of MPO, as observed in our study, are considered a significant inflammatory and oxidative stress marker in several diseases including lung injury.<sup>39,58</sup> MPO protein released from activated neutrophils acts as an auto-crine modulator, exhibiting proinflammatory cytokine-like properties to induce PMN activation, in a manner that is independent of MPO catalytic activity.<sup>59</sup> Thus, in the light of these reports and our present findings, we posit that chronic CBD aerosol-inhalation could induce a strong proinflammatory microenvironment that could be more detrimental to pulmonary homeostasis and might further aggravate existing lung diseases. Neutrophil infiltration to the lungs after CBD aerosol-inhalation might possibly be induced by the upregulation of soluble chemokines like KC, and thus could be responsible for enhanced levels of NE found in the BAL and lung tissue. Since CBD aerosol-exposure induced the release of NE from human neutrophils in vitro, this supports the conclusion that CBD aerosols have the potential to directly activate neutrophils in vivo and augment pulmonary inflammation in users. As the levels of NE and associated activity increase during neutrophil-mediated inflammatory responses,<sup>46</sup> we thus only measured the levels of NE as an index of its activity. Additionally, the detrimental impact of vaping CBD could likely be exacerbated by impaired antioxidant systems as we observed, where factors like CBD-Vape-induced MPO could play critical roles.<sup>39,58</sup>

CD4<sup>+</sup>RORγt<sup>+</sup> T cells, which express the master transcription factor essential for the differentiation into proinflammatory Th17 cells, were augmented and predict a proinflammatory microenvironment induced by CBD aerosols. Increased induction of CD4<sup>+</sup>FoxP3<sup>+</sup> T regulatory cells (Tregs) might be one mechanism by which CBD vaping could induce immunosuppression. Tregs suppress activation, proliferation and cytokine production of CD4<sup>+</sup> and CD8<sup>+</sup> T cells and are implicated in suppressing dendritic cells via downregulating costimulatory molecules.<sup>60</sup> Tregs express the IL-2 receptor α-chain, which facilitates IL-2 consumption and thus could deprive T effector cells of IL-2 availability, contributing

**Table 2** Comparison of various markers of study outcomes after exposure to CBD-containing vaping product (CBD-vape) and nicotine-containing vaping product (Nic-vape)

| Study outcomes                           | Markers                                                                        | Results CBD-Vape vs Nic-Vape               |
|------------------------------------------|--------------------------------------------------------------------------------|--------------------------------------------|
| 1. Lung damage                           | Total protein levels in BAL                                                    | Equivalent                                 |
|                                          | FITC-dextran levels in blood                                                   | More in CBD-Vape (****)                    |
|                                          | Albumin levels in BAL                                                          | More in CBD-Vape (****)                    |
|                                          | NE levels in BAL                                                               | Equivalent                                 |
|                                          | NE levels in lungs                                                             | More in CBD-Vape (**)                      |
|                                          | MPO activity in BAL                                                            | Equivalent                                 |
|                                          | MPO activity in lungs                                                          | More in CBD-Vape (**)                      |
| 2. Inflammatory markers                  | IL-6                                                                           | More CBD-Vape (***)                        |
|                                          | IL1alpha                                                                       | Equivalent                                 |
|                                          | G-CSF                                                                          | More in CBD-Vape (**)                      |
|                                          | IL-5                                                                           | More in CBD-Vape (**)                      |
|                                          | KC                                                                             | Equivalent                                 |
|                                          | IL-2                                                                           | Equivalent                                 |
|                                          | IL-10                                                                          | Equivalent                                 |
| 3. Immune cells                          | IFN- $\gamma$                                                                  | Equivalent                                 |
|                                          | Total lung immune infiltrate                                                   | More in CBD-Vape (*)                       |
|                                          | # of Neutrophils                                                               | Equivalent                                 |
|                                          | # of CD8 <sup>+</sup> T cells                                                  | More in CBD-Vape (***)                     |
|                                          | # of CD4 <sup>+</sup> T cells                                                  | More in CBD-Vape (****)                    |
|                                          | # of CD19 <sup>+</sup> B cells/gm lung                                         | Equivalent                                 |
|                                          | # of CD4 <sup>+</sup> IL-17A <sup>+</sup> T cells/gm lung                      | Equivalent                                 |
|                                          | # of CD4 <sup>+</sup> RORgt <sup>+</sup> T cells/gm lung                       | More in CBD-Vape (****)                    |
|                                          | # of CD4 <sup>+</sup> Foxp3 <sup>+</sup> T cells/gm lung                       | More in CBD-Vape (***)                     |
|                                          | # of CD11c <sup>+</sup> Siglec-F <sup>+</sup> macrophages/gm of lung           | Equivalent                                 |
|                                          | # of CD11c <sup>+</sup> CD206 <sup>+</sup> interstitial macrophages/gm of lung | Less in CBD-Vape (*)                       |
|                                          | # of CD11c <sup>+</sup> Arginase-1 <sup>+</sup> macrophages/gm of lung         | Less in CBD-Vape (*)                       |
| 3. Histology                             | Granulocytes                                                                   | Frequency and severity greater in CBD-Vape |
|                                          | Macrophages                                                                    | Frequency and severity greater in CBD-Vape |
|                                          | Lymphocytes                                                                    | Frequency and severity greater in CBD-Vape |
|                                          | Lipid-containing, intra-alveolar macrophages                                   | Equivalent                                 |
| 4. Oxidative stress                      | Total antioxidant levels in lungs and BAL                                      | Equivalent                                 |
| 5. Small airway epithelial cell toxicity | Cell death                                                                     | Higher but not significant                 |
|                                          | Epithelial barrier integrity disruption                                        | Higher but not significant                 |
| 6. Human neutrophil dysfunction          | Higher but not significant                                                     | More in CBD-Vape (***)                     |
|                                          | Apoptotic cell death                                                           | More in CBD-Vape (***)                     |
|                                          | NE release in condition media                                                  | More in CBD-Vape (*)                       |

Non-parametric Kruskal-Wallis test with FDR correction for multiple comparisons was performed to see if statistically significant differences exist between CBD-Vape vs Nic-Vape for various parameters measured in the study using GraphPad Prism V.9 software (GraphPad; La Jolla, California, USA). The difference between two groups was considered significant at  $p < 0.05$  obtained when FDR was set at  $Q < 0.1$  and are indicated with the symbols.  
 \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$ , \*\*\*\* $p < 0.0001$ .  
 CBD, cannabidiol; FDR, false discovery rate; NE, neutrophil elastase.

to T effector cell suppression.<sup>61</sup> Thus, decreased IL-2 levels in the BAL due to CBD aerosol-induced augmentation of Tregs could mediate T cell dysfunction and suppression of adaptive immunity in the lungs, increase susceptibility to respiratory infections and induce poor outcomes to prophylactic vaccination.

We observed a significant reduction in the number of lung interstitial macrophages after exposure to CBD. Siglec-F<sup>+</sup>, typically considered an eosinophil marker, is highly expressed in murine alveolar macrophages, and when used in combination with CD11c, provides the most accurate identification of alveolar macrophages in the mouse lung. The significant reduction in the numbers of CD11b-CD11c<sup>+</sup>Siglec-F<sup>+</sup> alveolar macrophages observed in mice exposed to CBD is supported by previous studies.<sup>62</sup> An earlier study reported that EC exposure in mice induced alveolar macrophage dysfunction associated with poor pathogen uptake, with concomitant enhancement of pulmonary pathogen burden that correlated with delayed recovery time and increased mortality

after infection.<sup>16</sup> A marked decrease in the numbers of anti-inflammatory pulmonary arginase-1<sup>+</sup> M2 macrophages following CBD aerosol-inhalation could further contribute to dysregulated pulmonary immune homeostasis and damage.<sup>63</sup> The heightened proinflammatory microenvironment detected in the lungs following CBD inhalation could be partly attributed to the reduced numbers of anti-inflammatory M2 pulmonary macrophages. Diminished numbers of macrophages could significantly impact pulmonary responses to respiratory infections, which can be compounded by dysfunctional macrophage-phagocytosis. Thus, exposure to aerosols from nicotine-containing electronic cigarettes induced a reduction in phagocytosis of non-typeable *Haemophilus influenza* (NTHI) by macrophages, largely due to the presence of e-cigarette flavourings.<sup>64</sup> Since, common flavourings are also used for CBD formulations, it raises the possibility that CBD aerosol-induced macrophage dysfunction could be intensified with the addition of various flavouring chemicals.

The presence of lipid laden intra-alveolar macrophages observed in cells recovered from the BAL of mice after CBD aerosol-inhalation in our study corroborates with a previous report that showed the onset of exogenous lipid pneumonia in a patient who vaped cannabis oils and had lipid laden lung macrophages.<sup>65</sup> As exogenous lipid pneumonia with lipid-laden lung macrophages is a hallmark of EVALI, it thus suggests that inhalation of CBD vape oil might not be risk-free and could lead to lung injury in cannabis vapers. The cases presented in EVALI clinical reports suggested a stronger aetiological link between cannabis vaping and respiratory failure compared with nicotine vaping.<sup>65–68</sup> In contrast to our earlier studies in mice that inhaled VEA (the likely cause of EVALI), in this study, we did not observe the presence of foamy macrophages.<sup>14</sup> While the overall risks for pulmonary complications associated with vaping may be lower compared with smoking, vaping appears to pose a respiratory health risk, especially in long-term cannabis vapers.

In summary, our study clearly establishes that a proinflammatory milieu in the lungs induced by CBD aerosol-inhalation was greater than that induced by nicotine aerosols, and this was reflected by pulmonary barrier integrity disruption and lung damage (summarised in table 2). This suggests that cannabis vaping could potentially lead to more severe outcomes, including increased susceptibility to respiratory infections, poor responses to prophylactic vaccinations and worsening of symptoms in patients with underlying pulmonary inflammatory diseases.<sup>16–19 35 36 69 70</sup> We did not observe any visible changes in animal behaviour during or after the exposures, nor weight changes compared with air control (online supplemental figure E11). In this study, nicotine aerosol-exposure did not induce the levels of various cytokines/chemokines in the BAL to the same extent when compared with a previous study.<sup>71</sup> Reasons for this discrepancy could be that these authors measured the transcript levels of various cytokines in lung homogenates following nicotine-aerosol exposures, and transcript levels sometimes do not translate to changes when measured at the protein levels as done by us. Furthermore, cytokine profile and immune system modulation are dependent on the specific e-liquid, method of aerosol generation/exposure duration, and flavouring chemicals added. While cannabis has proven health benefits in pain management, sleep, relieving the symptoms of chemotherapy-induced nausea/vomiting in cancer patients and in patients experiencing seizures,<sup>72–76</sup> there is simply a lack of robust evidence about cannabis safety when delivered from vaping products. In this regard, our study is novel and identifies the role of CBD aerosol-inhalation in inducing pulmonary inflammation and lung damage.

Since our study used animal and in vitro exposure models, several limitations need to be considered when extrapolating results presented to real-life exposure in humans. One limitation of this study is its focus was only on short-term exposure. The outcome of long-term chronic exposure to CBD-aerosols, and their impact on responses to respiratory infection and/or prophylactic vaccination are of importance. Our animal exposure methodology was based on whole-body exposure system and nose-only exposure may perhaps be more suitable to simulate exposure of experienced vapers. Despite using whole-body exposure system, we verified that deposition on animal fur (and cage walls) did not contribute to ingestion of particulates by animal grooming and thereby influence the toxicity observed. We used a limited number of mice per exposure group; it is likely that larger numbers of mice could have further strengthened our study conclusions. Although the in vitro ALI model provides an inhalation exposure-specific approach for performing the biological study on health effects related to use of vaping products, extrapolating data from in vitro studies to human risks remains hypothetical. Future observational and experimental studies with regular users of CBD and nicotine-containing vaping products are needed to confirm our findings. Finally, in our experiments, animals and cells were exposed to aerosols from both products generated in an identical way. However, users of cannabis-based vaping products may use these products in a very different way than nicotine vapers (eg, less frequently). As data

from observational studies among cannabis vapers emerge, potential differences in product use patterns observed in realistic conditions should be taken into consideration when simulating animal and in vitro exposure in laboratory settings. Future studies should investigate respiratory effects of vaping products containing a wide spectrum of cannabinoids, including THC.

**Correction notice** This article has been corrected since it was published Online First. Table 1 has been corrected.

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## ARTIGO ORIGINAL

# Dose única de budesonida/formoterol turbuhaler comparada com salbutamol pMDI para a velocidade de início de ação de broncodilatador na asma: um ensaio aleatorizado cruzado

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## RESUMO

**Objetivo** Comparar a resposta do broncodilatador após o uso de salbutamol e budesonida/formoterol em adultos com asma estável.

**Métodos** Um ensaio clínico de não inferioridade, em dupla ocultação, cruzado, num único centro, controlado por placebo. Adultos com asma estável foram aleatorizados para dois regimes de tratamento: duas atuações de placebo via MDI e uma atuação de budesonida/formoterol 200/6 µg via turbuhaler; e uma atuação de placebo turbuhaler e duas atuações de salbutamol 100 µg via MDI. A principal medida de resultado foi o FEV<sub>1</sub> após 2 minutos. Os resultados secundários incluíram o FEV<sub>1</sub>, a pontuação da Escala de Dispneia mBorg e a pontuação visual analógica para dispneia ao longo de 30 minutos.

**Resultados** Foram aleatorizados quarenta e nove dos 50 potenciais participantes. Um participante desistiu após a primeira visita de intervenção e outro não pôde ser aleatorizado devido às restrições da COVID-19. A alteração média (DP) do FEV<sub>1</sub> basal 2 minutos após a administração do tratamento para budesonida/formoterol e salbutamol foi de 0,08 (0,14) L, n=49, e 0,17 (0,18) L, n=48, respetivamente, diferença média (IC 95%) emparelhada de -0,097 L (-0,147 a -0,047), p=0,07, contra um limite de não inferioridade de -0,06 L. Na análise secundária, o VEF1 ao longo de 30 minutos foi menor para budesonida/formoterol em comparação com salbutamol, diferença (IC 95%): -0,10 (-0,12 a -0,08) L, p<0,001. Não se registaram diferenças na pontuação da Escala Visual Analógica ou na pontuação da Escala de Dispneia mBorg entre os tratamentos.

**Conclusão** Os resultados não apoiam a hipótese primária de não-inferioridade no limite de -0,06 L para a diferença entre budesonida/formoterol 200/6 µg em comparação com salbutamol 200 µg para FEV<sub>1</sub> a 2 min, e podem ser consistentes com inferioridade com um valor p de 0,07. Para a análise secundária das medições de FEV<sub>1</sub> ao longo do tempo, o FEV<sub>1</sub> foi mais elevado com salbutamol.

**Número de registo do ensaio** Registo de Ensaios Clínicos da Austrália e da Nova Zelândia (ACTRN 12619001387112).

## INTRODUCTION

Budesonide-formoterol reliever therapy is superior to short-acting beta<sub>2</sub>-agonist (SABA) reliever therapy in adults and adolescents with asthma, across the range of asthma severity.<sup>1–5</sup> As needed budesonide-formoterol therapy reduces the relative risk of severe exacerbations by over one half compared with SABA reliever therapy in mild asthma,<sup>5–7</sup> by 15% compared with maintenance budesonide plus SABA reliever,<sup>1</sup> and by about one third compared with SABA reliever in patients taking maintenance inhaled corticosteroid/long-acting beta<sub>2</sub>-agonist (ICS/LABA).<sup>2,3</sup> In a network meta-analysis, low and medium dose ICS/formo-

## Key messages

### What is the key question?

► Combination inhaled corticosteroid-formoterol is the preferred reliever to short-acting beta<sub>2</sub>-agonist (SABA) for adults and adolescents with any severity of asthma. A potential concern with budesonide/formoterol reliever monotherapy is that patients switching from a SABA to budesonide/formoterol may fail to achieve similar fast and effective symptom relief. As such, it is crucial that both clinicians and patients have confidence in the speed of onset of the bronchodilator effects of budesonide-formoterol in comparison to salbutamol, when used as a reliever.

### What is the bottom line?

► There was no evidence of non-inferiority at a boundary of -0.06 L for the difference between budesonide/formoterol 200/6 µg compared with salbutamol 200 µg for FEV<sub>1</sub> at 2 min, although the results could be consistent with inferiority with a p value of 0.07. For FEV<sub>1</sub> measurements over the 30-min time course, the FEV<sub>1</sub> was higher with salbutamol.

### Why read on?

► This is the first study to investigate the comparative speed of onset of bronchodilation of budesonide/formoterol and salbutamol, which is of clinical importance due to the recommended use of budesonide/formoterol as a reliever therapy in asthma.

terol maintenance and reliever therapy (SMART) were ranked higher than all other therapeutic regimens including low, medium and high dose ICS/LABA maintenance plus SABA reliever therapy, and ICS/formoterol alone was ranked higher than low and medium dose ICS and low dose ICS/LABA plus SABA reliever therapy.<sup>3</sup>

In clinical trials, this reduction in severe exacerbation risk is seen with self-administered use of ICS/formoterol by patients in the long-term treatment of asthma in the community setting. Based on this evidence, the Global Initiative for Asthma (GINA) recommends that combination ICS-formoterol is the preferred reliever for adults and adolescents with any severity of asthma.<sup>8,9</sup>

A potential concern with budesonide/formoterol reliever monotherapy is that patients switching from a SABA to budesonide/formoterol may fail to achieve similar fast and effective symptom relief. As such, it is crucial that both clinicians and patients have confidence in the speed of onset of the bronchodilator effects of budesonide-formoterol in comparison to salbutamol, when used as a reliever. There is evidence that formoterol 6 µg turbuhaler results in a similar speed of onset as salbutamol 200 µg via pressurised metered-dose inhaler (pMDI),<sup>10</sup> however, comparative studies of a single dose of bronchodilator speed of onset of budesonide-formoterol compared with salbutamol have not been reported in adult asthma.

We have recently shown that with repeated dosing, salbutamol 200 µg results in a greater magnitude of acute bronchodilation than budesonide/formoterol 200/6 µg in adults with stable asthma.<sup>11</sup> In this companion study, we have compared the magnitude of bronchodilation after 2 min of administration of a single dose of salbutamol 200 µg and budesonide/formoterol 200/6 µg. Our hypothesis was that the bronchodilator efficacy of budesonide/formoterol is non-inferior to salbutamol.

## MATERIALS AND METHODS

### Study design and participants

This was an investigator-led, double-dummy, double-blind, cross-over, single-centre, randomised controlled trial comparing salbutamol with budesonide/formoterol conducted at the Medical Research Institute of New Zealand (MRINZ). The trial was run in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki.

Adults with asthma aged 18–65 years, with an  $FEV_1 > 50\%$  predicted and bronchodilator reversibility with an  $FEV_1 \geq 10\%$  and  $\geq 200$  mL were recruited. Details of inclusion and exclusion criteria are in table 1 in the online supplemental file. Participants were required to withhold their SABA inhalers for 6 hours, LABA inhalers for 24 hours and ultra-LABA inhalers for 48 hours prior to each visit. Written informed consent was obtained from all participants. Study data were collected and managed using REDCap (Research Electronic Data Capture) hosted at MRINZ.<sup>12 13</sup>

### Procedures

Participants attended an initial screening visit to determine eligibility and then returned on a different day for randomisation and first intervention visit, followed by a second intervention visit after a minimum washout period of 2 days. A  $FEV_1$  within 12% of the  $FEV_1$  volume at screening was required on both intervention visit days prior to treatment administration. If the  $FEV_1$  failed to fall within 12%, participants reattended on a different day for their study visit.

Spirometry (Care Fusion MasterScope non-heated pneumotach spirometer running software V5.32.0) was measured according to American Thoracic Society/European Respiratory Society guidelines.<sup>14 15</sup>  $FEV_1$  was assessed at baseline (–15 to –2 min) and 1, 2, 3, 5, 10, 15 and 30 min after treatment administration.

The Modified Borg Dyspnoea Scale score (mBorg)<sup>16 17</sup> rated from '0: Nothing at all' to '10: Maximal' was used to assess breathlessness at baseline and at 10 and 30 min after treatment administration. The Visual Analogue Scale (VAS) Score,<sup>18 19</sup> a horizontal 100 mm line with 'very much worse' and 'very much better' at each end and a marker of 'no change' in the middle was also used to assess breathlessness at 1, 2, 3, 5, 10, 15 and 30 min after treatment administration. Participants were instructed to place a vertical line on the point that most accurately expressed their breathlessness when compared with baseline on the same day. The mBorg and VAS scores were assessed prior to performing spirometry at the relevant timepoints. At the screening visit and prior to both interventions, participants were trained in and then asked to demonstrate the correct inhaler technique using In-Check DIAL G16<sup>20</sup> for both the Turbuhaler and the pMDI inhaler without a spacer.

## Interventions

The budesonide/formoterol arm was two actuations of placebo pMDI (Norflurane CFC-Free MDI, GlaxoSmithKline), followed by one actuation of budesonide/formoterol (Symbicort Turbuhaler 200 µg of budesonide and 6 µg of formoterol; Astra-Zeneca). The time of bronchodilator administration (T0) was recorded as the time the actuation of budesonide/formoterol was given.

The salbutamol arm was one actuation of placebo turbuhaler (AstraZeneca), followed by two actuations of salbutamol (Ventolin 100 µg CFC-Free MDI, GlaxoSmithKline). The time of bronchodilator administration (T0) was recorded as the time the second actuation of salbutamol was given.

## Outcomes

The primary outcome measure was  $FEV_1$  after 2 min. Secondary outcome measures were  $FEV_1$  after 1, 3, 5, 10, 15 and 30 min; mBorg Dyspnoea Scale score after 10 and 30 min and VAS after 1, 2, 3, 5, 10, 15 and 30 min.

## Sample size

In a feasibility study with a cross-over design,<sup>21</sup> the SD for paired  $FEV_1$  measurements was approximately 160 mL (at both 2 and 5 min). The non-inferiority bound was set at –60 mL, equivalent to approximately 25% of the minimal 'perceivable improvement' of 230 mL.<sup>22</sup> With a paired t-test assessment for the difference, at 80% power and a one-sided alpha of 5%, 46 participants would be required, based on a paired SD of 160 mL. To allow for an 8% dropout rate, 50 participants would be needed.

## Randomisation

Participants were randomised 1:1 to different orders of the intervention arms in an AB/BA cross-over design. The randomisation method involved a computer-generated sequence supplied by the study statistician, independent of the investigators. The sequence was uploaded into REDCap by an individual who was otherwise uninvolved in study processes. REDCap concealed the allocations until after randomisation. Treatment allocation was only visible to unblinded investigators who conducted randomisation and administration of treatment. Blinded investigators conducted all other study procedures including those related to outcome measures. Participants remained blinded to their treatment allocation.

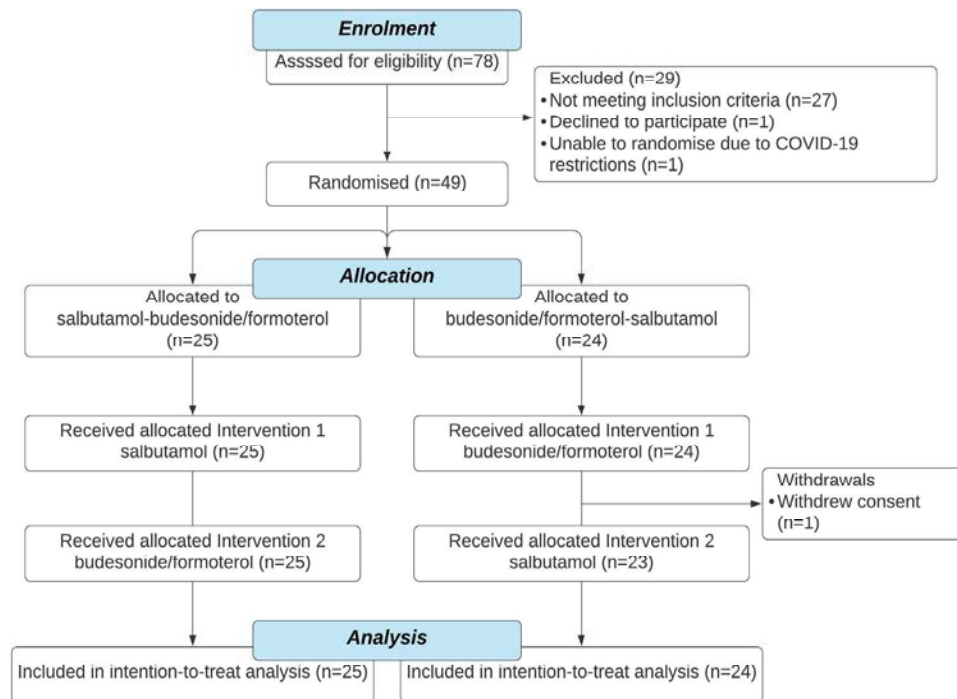
## Statistical methods

For the primary analysis, a mixed linear model was used with fixed effects of treatment, treatment order and baseline value, and random effect for participant (to take into account the cross-over design). The assumptions for the linear mixed model were met. For the main research question the primary hypothesis test of non-inferiority was based on the nominated non-inferiority bound of 0.06 L. For the secondary comparisons comparing the treatments 95% CI are shown and the p values reflect a test of whether the differences between the treatments was 0.

For the secondary analyses, mixed linear models were also used with an additional fixed effect for time and a time by treatment interaction. As a sensitivity analysis, participants with protocol violations were removed from the analysis dataset for the primary analysis. SAS V9.4 was used.

## RESULTS

Forty-nine participants were randomised (figure 1) between 9 January 2020 and 21 June 2021. The trial was paused from 22 March 2020 to 26 June 2020 in accordance with the New Zealand government's COVID-19 response. One participant withdrew consent following the first intervention visit (budesonide/formoterol arm). We were unable to randomise the last (50th) participant due to a new onset of COVID-19 government restrictions on 23 June 2021. As the study had already exceeded its prespecified recruitment aim of 46 participants, and because of the uncertain nature of the pandemic, the trial management group decided to end the study after randomisation of 49 participants. All participants with data



**Figure 1** Consolidated Standards of Reporting Trials flow diagram.

were included in the intention-to-treat analysis. Baseline characteristics are shown in table 1. At baseline, participants had a mean (SD) FEV<sub>1</sub> percent predicted 72.6% (13.2), mean (SD) FEV<sub>1</sub> bronchodilator reversibility of 18.8% (6.5), and an mBorg Dyspnoea Scale score of 3.1 (1.5).

In the primary analysis, there was no evidence for non-inferiority for the difference between budesonide/formoterol compared with salbutamol for FEV<sub>1</sub> at 2 min. The mean (SD) change from baseline FEV<sub>1</sub> 2 min after treatment administration for budesonide/formoterol and salbutamol was 0.08 (0.14) L, n=49, and 0.17 (0.18) L, n=48, respectively, with a mean (95% CI) paired difference of -0.097 (-0.147 to -0.047) L, p=0.07 against non-inferiority bound of -0.06. The FEV<sub>1</sub> at each time point for the budesonide/formoterol and salbutamol interventions are shown in figure 2.

The point estimates and 95% CIs from linear mixed models at each time point with test for non-inferiority (P non-inferiority), testing against a one-sided limit of -0.06 L; and superiority (P superiority), as a two-sided test against 0 are shown in figure 3. In the secondary analysis, using all measurement times in a mixed linear model, there was no evidence that the differences in FEV<sub>1</sub> between treatments depended on the time of measurement, p=0.88. As none of the time by treatment interaction terms were significant, the overall difference averaged over all the time points is a better representation of the difference between treatments. When averaged over all the time points, FEV<sub>1</sub> was lower in the budesonide/formoterol group compared with the salbutamol group, estimated difference (95% CI): -0.10 (-0.12 to -0.08) L, p<0.001 based on testing the differences between treatment against 0. For illustrative purposes the individual treatment differences by time are also shown in table 2 based on a model that includes a time by treatment interaction term.

There was no evidence of differences in the VAS or mBorg Dyspnoea Scale score between treatments (figures 4 and 5). When averaged over time, the estimated difference in VAS scores for budesonide/formoterol minus salbutamol (95% CI) was -1 (-2.3 to 0.2) L, p=0.10; and for the mBorg Dyspnoea Scale -0.15 (-0.02 to 0.33) L, p=0.10. There was no evidence that the VAS and mBorg Dyspnoea Scale scores in the two treatment groups were different at different time points.

There were 33 adverse events reported in 22 participants. Only one event (headache) was thought to be related to the administration of salbutamol. One participant experienced a mild worsening of their asthma while withholding their inhalers for the study

visit which resolved following self-administration of their reliever therapy. There were no serious adverse events.

## DISCUSSION

This randomised controlled trial found no evidence of non-inferiority against a boundary of an FEV<sub>1</sub> of -0.06 L for the difference between budesonide/formoterol 200/6 µg compared with salbutamol 200 µg at the time point of 2 min. However, the p value for non-inferiority was 0.07 and the upper confidence bound of the comparison was close to the boundary of 0.06 L, and this could be consistent with inferiority. In the secondary analysis, when averaged over time, there was strong evidence the FEV<sub>1</sub> was 0.10 L higher in the salbutamol group, and the upper confidence bound was less than the prespecified non-inferiority bound. There were no differences in the measures of breathlessness between the two interventions.

Previous studies reporting differences between formoterol and salbutamol in the outpatient setting are difficult to interpret because they do not report differences in point estimates and CIs for differences in FEV<sub>1</sub>, use different doses or methods of treatment administration and have different time points for primary evaluation. One previous study comparing single doses of formoterol 4.5 µg (equivalent to the delivered dose of formoterol in Symbicort Turbuhaler 200/6) and 9 µg delivered via a turbuhaler and salbutamol 100 µg and 200 µg delivered via pMDI showed no difference between the treatments at the primary outcome of 3 min, with an increase in FEV<sub>1</sub> of 11.7%, 11.8%, 10.0% and 11.4% respectively.<sup>10</sup>

A similar study comparing formoterol 4.5 µg × 2 delivered via a pMDI and salbutamol 200 µg delivered via pMDI showed no difference in FEV<sub>1</sub> between the two treatments at the primary outcome of 3 min, with a geometric mean ratio (95% CI) of 1.00 (0.98, 1.02).<sup>23</sup> In a third study, comparing single doses of formoterol (12, 24 and 48 µg) via a pMDI with salbutamol 200 µg also delivered by a pMDI, specific airways conductance increased at 1, 3 and 5 min after all active treatments.<sup>24</sup> When the bronchodilator effect was expressed as a percentage of the maximum response, the rate of onset after salbutamol was more rapid than after formoterol.

Another model to compare the speed of onset of bronchodilator action is administration following methacholine-induced bronchoconstriction. Using this model, the FEV<sub>1</sub> after the first minute was greater following salbutamol 200 µg delivered via pMDI compared with budesonide/formoterol 160/4.5 µg via turbuhaler

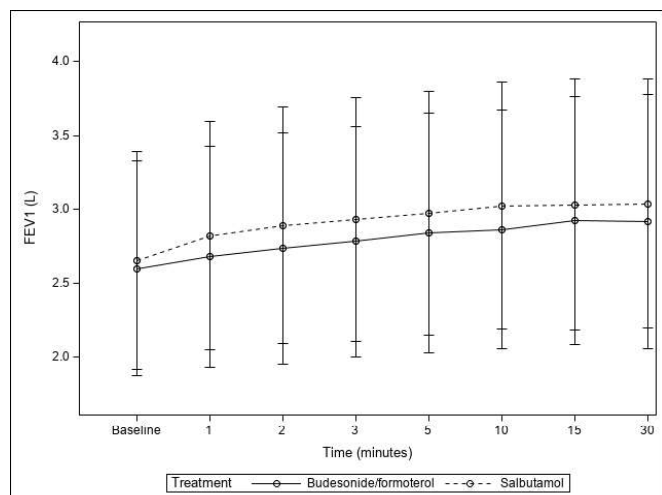
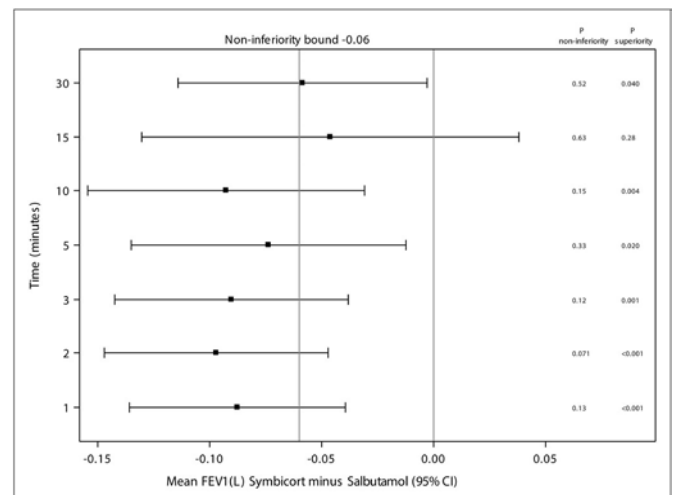
**Table 1** Baseline characteristics of study population

| Characteristics                                 |               |
|-------------------------------------------------|---------------|
| Continuous variables n=49                       | Mean (SD)     |
| Age (years)                                     | 38.0 (13.7)   |
| Age at asthma diagnosis (years)                 | 10.2 (10.1)   |
| Pack years tobacco smoking                      | 1.3 (2.3)     |
| Lung function                                   |               |
| FEV <sub>1</sub> (L)                            | 2.6 (0.8)     |
| FEV <sub>1</sub> (per cent predicted)           | 72.6 (13.2)   |
| FEV <sub>1</sub> reversibility (mL)             | 477.6 (176.3) |
| FEV <sub>1</sub> reversibility (percentage)     | 18.8 (6.5)    |
| Modified Borg Dyspnoea score                    | 3.1 (1.5)     |
| Categorical variables                           | N/49 (%)      |
| Sex                                             |               |
| Female                                          | 29 (59.2)     |
| Male                                            | 20 (40.8)     |
| Ethnicity*                                      |               |
| European                                        | 38 (77.5)     |
| Māori                                           | 5 (10.2)      |
| Asian                                           | 5 (10.2)      |
| Pacific people                                  | 1 (2.0)       |
| Smoking status                                  |               |
| Ex-smoker                                       | 12 (24.5)     |
| Never                                           | 37 (75.5)     |
| Medication use                                  |               |
| Patient-reported use of SABA only at enrolment  | 12 (24.5)     |
| Patient-reported use of ICS + SABA at enrolment | 4 (8.1)       |
| Patient use of ICS/LABA only at enrolment       | 16 (32.7)     |
| Patient use of ICS/LABA + SABA at enrolment     | 17 (34.7)     |

\*Prioritised ethnicity using level 1 codes.<sup>17</sup>

ICS, inhaled corticosteroid; LABA, long-acting beta<sub>2</sub>-agonist; SABA, short-acting beta<sub>2</sub>-agonist.

(0.39 L vs 0.30 L,  $p=0.03$ ), whereas over the entire remaining recovery period, similar increases in FEV<sub>1</sub> were observed.<sup>25</sup> In a similar study, formoterol 12 µg and salbutamol 200 µg delivered by pMDI both achieved pre-methacholine levels of specific airways conductance within 3 min.<sup>26</sup> Similarly, formoterol 12 µg and 24 µg, and salbutamol 400 µg, via a dry powder inhaler (DPI) resulted in similar improvements in FEV<sub>1</sub> at 2 min, with mean recovery times to 50% of the FEV<sub>1</sub> decrement provoked by methacholine achieved

**Figure 2** Time course of FEV<sub>1</sub> for budesonide/formoterol and salbutamol.

**Figure 3** Point estimates and CIs from linear mixed models at each time point with test for non-inferiority ( $p$  non-inferiority), testing against a one-sided limit of  $-0.06$  L: and superiority ( $p$  superiority), as a two-sided test against 0. The primary analysis was at the 2 min time point. The interpretation is that for non-inferiority, the lower confidence limit for the comparison must be to the right of the non-inferiority bound. The  $p$  non-inferiority tests this, and if the point estimate is to the right of the bound and  $p$  non-inferiority is  $<0.05$  this is evidence for non-inferiority. However, in this case on this plot the upper confidence limit is to the left of the non-inferiority bound on the plot, and the upper confidence limit as also close to the non-inferiority bound with  $p=0.07$  which is weak evidence for inferiority at time=2 min. The  $p$  superiority tests against 0; namely is there evidence against the null hypothesis of no difference, and on the plot this is where the upper confidence limit is to the left of 0, seen for all individual time-points except 15 min.

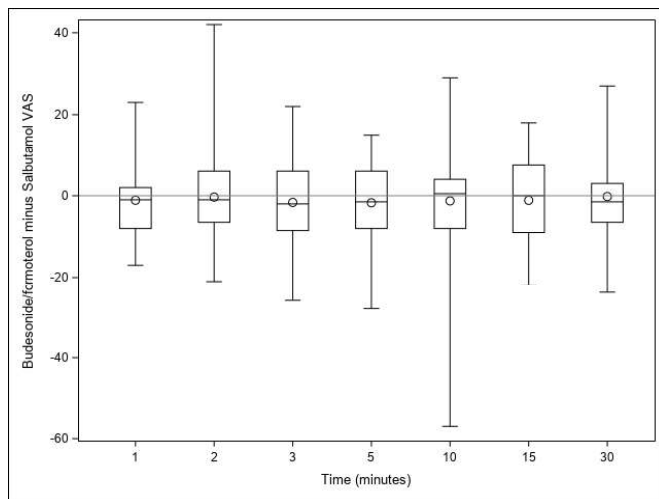
within 10.2, 5.7 and 6.4 min for formoterol 12 µg, 24 µg and salbutamol 400 µg, respectively.<sup>27</sup> In a fourth study, formoterol 12 µg via a DPI and salbutamol 50 µg via a DPI resulted in comparable times for the FEV<sub>1</sub> to return to 85% of baseline; 7.2 vs 6.5 min, respectively.<sup>28</sup>

Relevant to the interpretation of these and our current findings is the issue as to equivalent bronchodilator doses. In a companion study, we have shown that following repeated doses, salbutamol 200 µg results in a greater magnitude of acute bronchodilation than budesonide/formoterol 200/6 µg.<sup>11</sup> At these comparative doses, salbutamol results in a greater fall in serum potassium, a systemic beta<sub>2</sub>-agonist effect,<sup>29</sup> and in addition a higher heart rate and more adverse effects. While our current findings on the speed of onset of bronchodilation are generalisable to the doses recommended in clinical practice, it would also be informative to determine this outcome for equivalent beta<sub>2</sub>-agonist doses.

There are a number of methodological issues relevant to the interpretation of the findings. First, we used a model of adults with mild to moderate asthma and demonstrable reversible airflow obstruction in an outpatient clinic situation instead of those

**Table 2** Secondary analyses of FEV<sub>1</sub> comparison at all time points

| Time (minutes)          | Budesonide/formoterol minus Salbutamol Difference (95% CI) | P value (vs 0) |
|-------------------------|------------------------------------------------------------|----------------|
| 1                       | -0.11 (-0.16 to -0.05)                                     | <0.001         |
| 2                       | -0.12 (-0.17 to -0.06)                                     | <0.001         |
| 3                       | -0.11 (-0.17 to -0.05)                                     | <0.001         |
| 5                       | -0.095 (-0.15 to -0.07)                                    | 0.001          |
| 10                      | -0.11 (-0.17 to -0.06)                                     | <0.001         |
| 15                      | -0.07 (-0.12 to -0.01)                                     | 0.02           |
| 30                      | -0.08 (-0.14 to -0.03)                                     | 0.004          |
| Averaged over all times | -0.10 (-0.12 to -0.08)                                     | <0.001         |

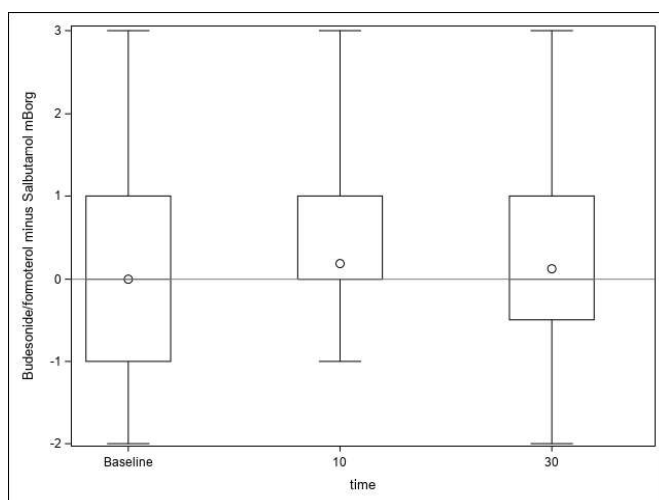


**Figure 4** Time course for difference in VAS over time, budesonide/formoterol minus salbutamol. On the Y axis, a positive number favours budesonide/formoterol and a negative number favours salbutamol. VAS, Visual Analogue Scale

acutely requiring reliever therapy. The outpatient setting enabled a crossover study with stable baseline airflow obstruction, and was relevant to their use as reliever rather than a rescue therapy. The inclusion criteria requiring at least 10% bronchodilator reversibility ensured there was the capability to potentially demonstrate non-inferiority relevant to a minimal clinically important difference (MCID). However, as we excluded participants with an  $FEV_1$  <50% predicted, the findings may have limited generalisability to adults with severe airflow obstruction.

Second, although this was a double-blind study, participants may have been able to taste the difference between the placebo treatments and active treatments resulting in performance bias. However, all study outcomes were assessed by blinded investigators and it is unlikely that such a bias would affect physiological outcomes such as  $FEV_1$ .

Third, we powered the study to be able to determine a non-inferiority bound of  $-60$  mL, equivalent to approximately 25% of the minimal 'perceivable improvement' of 230 mL.<sup>22</sup> While to some extent this is an arbitrary non-inferiority bound, it can be considered a conservative estimate, recognising that the MCID of 230 mL would not be achieved within 2 min. Thus, the objective was not to determine whether there was a clinically important difference, but rather to examine non-inferiority. The analysis presented in figure 3 enables readers to interpret the findings in relation to alternative non-inferiority bounds.



**Figure 5** Time course for difference in modified Borg Dyspnoea Scale score over time, budesonide/formoterol minus salbutamol. On the Y axis, a positive number favours budesonide/formoterol and a negative number favours salbutamol.

It is also informative to compare the 100 mL higher  $FEV_1$  following salbutamol over the 30 min time period of the study with the MCID of 230 mL. This comparison provides an explanation as to why this magnitude of difference in lung function was not perceived by patients using the mBORG or VAS breathlessness scores. The point estimate of the difference in  $FEV_1$  detected in this study was less than half of the minimal 'perceivable improvement'.

Fourth, it is recognised that use of placebo pMDI or DPI may variably result in bronchoconstriction, bronchodilation or no immediate change in lung function.<sup>10 23 24 30</sup> In this study, the placebo inhalers (either two puffs of placebo pMDI or one puff of placebo turbuhaler) were given first, followed by the active drug. As a result, any effect of the respiratory manoeuvres on lung function with the different devices is likely to be well balanced between the randomised treatments.

The findings have three main clinical implications. The first is that for  $FEV_1$  measurements over the 30 min time course of the study, there was evidence of  $FEV_1$  being higher with salbutamol. This lesser degree of bronchodilation with budesonide/formoterol compared with salbutamol when administered in these relative doses recommended in clinical practice is unlikely to be of clinical importance, as the upper 95% CI in the  $FEV_1$  difference of 100 mL is about half the MCID of 230 mL.

The second clinical implication is that we could identify no difference in the degree of subjective breathlessness resulting from budesonide/formoterol compared with salbutamol when administered in these relative doses. This is important as it indicates that patients are unlikely to perceive any difference in the onset of, or magnitude of bronchodilation resulting from single doses of these bronchodilators, providing confidence for the transfer across from salbutamol to budesonide/formoterol as reliever therapy, in accordance with GINA recommendations.<sup>8</sup>

The third relates to their use in the long-term treatment of asthma, in which budesonide/formoterol 200/6 µg one actuation as needed reduces the risk of severe exacerbations compared with salbutamol 100 µg × 2, when either taken alone or together with ICS/LABA maintenance therapy.<sup>12 31</sup> Our study has shown that the greater efficacy with budesonide/formoterol is unlikely to be related to the speed of onset or magnitude of acute bronchodilator effects of budesonide/formoterol compared with salbutamol, although a contribution from its greater duration of action may be relevant.<sup>11</sup> These findings reinforce the importance of the ICS component of reliever therapy titrated according to changes in symptoms, through the vehicle of bronchodilator use to the efficacy of budesonide/formoterol reliever therapy.

In conclusion this study has shown no evidence of non-inferiority at a boundary point of  $-0.06$  L for the difference between budesonide/formoterol 200/6 µg compared with salbutamol 200 µg for  $FEV_1$  at 2 min; however, the results could be consistent with inferiority with a p value of 0.07. Over the 30-min time course, there was strong evidence of a higher  $FEV_1$  with salbutamol, but no difference in perceived breathlessness. These findings are of clinical importance due to the recommended use of budesonide/formoterol as a reliever therapy in asthma.

**Contributors** NK, MathewW, RB and IB were involved in the conception and design of the study. NK drafted the manuscript. NK, RB and MarkW contributed to the interpretation of data. NK, MathewW, PB, MB, CK and JS contributed to the acquisition of data. NK, MathewW, PB, MB, CK, JS, IB and RB were involved in the conduct of the study. MarkW was the study statistician. All authors contributed to the revision of the manuscript. NK and RB are guarantors for the manuscript.

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**Patient consent for publication** Not applicable.

**Ethics approval** This study was approved by the New Zealand Southern Health and Disability Ethics Committee (19/STH/170) and registered with the Australian and New Zealand Clinical Trials Registry (ACTRN 12619001387112).

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**Data availability statement** Individual participant data that underlie the results reported in this article, after de-identification (text, tables, figures, and appendices) will be available one year after publication until a minimum of 5 years after publication. It will be available to researchers who provide a methodologically sound proposal that has been approved by the study steering committee to achieve the aims outlined in the approved proposal. Data can be obtained through a signed data access agreement. The agreement can be obtained by emailing the Principal Investigator: richard.beasley@mrnz.ac.nz. The study protocol is available publicly on the ANZCTR website.

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## ARTIGO ORIGINAL

# Hospitalizações por asma e exposição ao calor em Inglaterra: um estudo de casos cruzados durante 2002-2019

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## RESUMO

**Contexto** Estudos anteriores referiram uma associação entre a temperatura quente e a hospitalização por asma. Estes estudos referiram diferentes vulnerabilidades relacionadas com o sexo e a idade; no entanto, pouco se sabe sobre a forma como este efeito se alterou ao longo do tempo e como varia no espaço. Este estudo tem como objetivo avaliar a associação entre a hospitalização por asma e a temperatura quente e investigar as vulnerabilidades por idade, sexo, tempo e espaço.

**Métodos** Recolhemos dados individuais sobre a hospitalização por asma no verão com elevada resolução temporal (diária) e espacial (códigos postais) durante 2002-2019 em Inglaterra a partir do NHS Digital. A temperatura média diária com resolução de 1 km x 1 km foi obtida a partir do UK Met Office. Concentramo-nos no período de 0-3 dias. Utilizamos um desenho de estudo de casos cruzados e aplicamos modelos de Poisson Bayesianos hierárquicos, tendo em conta possíveis fatores confundidores (precipitação, humidade relativa, velocidade do vento e feriados nacionais).

**Resultados** Depois de considerarmos os fatores confundidores, encontramos um aumento de 1,11% (intervalo de confiança de 95%: 0,88% a 1,34%) no risco de hospitalização por asma para cada aumento de 1°C na temperatura ambiente do verão. O efeito foi mais elevado nos homens com idades entre os 16 e os 64 anos (2,10%, 1,59% a 2,61%) e durante os primeiros anos da nossa análise. Também encontramos indícios de uma tendência linear decrescente do efeito ao longo do tempo. As populações de Yorkshire and the Humber e East and West Midlands foram as mais vulneráveis.

**Conclusão** Este estudo fornece evidências de uma associação entre a temperatura quente e a admissão hospitalar por asma. O efeito diminuiu ao longo do tempo, com possíveis explicações que incluem diferenças temporais nos padrões de exposição ao calor, mecanismos adaptativos, controlo da asma, estilo de vida, comorbilidades e ocupação.

## INTRODUCTION

Asthma is the second most prevalent chronic respiratory disease globally (3.6%) and the first in the Western world.<sup>1,2</sup> The prevalence of asthma in the UK is among the highest in the world with direct National Health Service (NHS) costs for managing asthma being estimated at £1 billion per annum with 12% of these costs being for hospital care.<sup>3,4</sup> Several risk factors, such as smoking, physical activity, medication, etc, have been known to trigger asthma symptoms.<sup>5</sup> In addition, environmental risk factors such as inhaling cold air, air pollutants and allergens can trigger asthma symptoms and exacerbations.<sup>5-7</sup> Previous studies have examined the role of warm temperatures on asthma hospitalisation, with the results being inconclusive.<sup>8-16</sup>

The impact of ambient warm temperature on asthma hospitalisation has received considerable

## Key messages

### What is already known on this topic

► Heat exposure has been reported to increase risk of asthma hospital admissions.

### What this study adds

► We assess the effect of warm temperatures on asthma hospitalisation using 18 years' worth of individual-level nationwide data in England. We examine vulnerabilities by age, sex, time and space and find an increased risk in males aged 16–64 (2.10%, 1.59% to 2.61%) and the early years of the study (2.96%, 2.56% to 3.37%) and the regions of Yorkshire and the Humber and West and East Midlands.

### How this study might affect research, practice or policy

► This study is the first to provide evidence that the effect of heat exposure in patients with asthma has attenuated over time. Potential reasons for this include temporal adaptation, differences in lifestyle, comorbidities and occupation.

attention recently.<sup>8-16</sup> Studies in Korea, Shanghai, China and the Los Angeles County, USA reported weak, if any, evidence of an association between increasing mean daily or maximum temperature and asthma hospitalisations.<sup>8,10,11</sup> In contrast, studies in Hong Kong, Himeji City, Japan, Taiwan, 1816 cities in Brazil, Maryland, USA, New York City, USA and Beijing, China reported an increased asthma hospitalisation risk with higher temperature especially during summer months.<sup>11,13,15-19</sup>

Some of the reasons contributing towards the above-mentioned discrepancies include decisions about the lags, temperature metrics, outcome definitions and selection of confounders, in addition to different adaptation mechanisms (eg, prevalence of air conditioning, building infrastructure, etc), population characteristics (eg, deprivation, age distribution, etc) and meteorology across the different countries. Methodological aspects might also limit the generalisability of previous studies. The temporal or geographical resolution in some of the previous studies is coarse leading to a less accurate exposure assignment; most studies examine daily hospitalisation with one study considering monthly hospitalisations,<sup>14</sup> and most previous studies assign exposure at the city level.<sup>15-17</sup> Most studies with individual data were conducted in urban settings, which limits the

generalisability of their results given that temperatures in urban settings are typically higher and less variable.<sup>15–17</sup> One study was nationwide in Taiwan, but the geographical resolution was coarse and the exposure available only at 25 meteorological stations.<sup>11</sup> Previous studies have examined effect modification by age and sex,<sup>15–17</sup> space<sup>8–11–16</sup> and by time,<sup>16</sup> but none considered all these dimensions together.

In this nationwide study in England, we examine the effect of ambient temperature on hospital admissions for asthma during 2002–2019. This study aims to address some of the limitations in previous studies by covering one of the largest temporal windows for asthma hospitalisations in the literature, using individual data and exploiting high geographical resolution to link outcome (~100 m) with the exposure (1 km). We account for different meteorological confounders and investigate how the effect of ambient temperature on asthma hospitalisations is modified by age and sex. We also examine how the effect is modified by time and region, as we expect the effect to have attenuated over time, for reasons including adaptation (including changes in behaviours, heat-health warnings, etc), improvement in asthma treatment and awareness of asthma management, etc, and to be different across space (due to factors that might also vary in space such as differences in green space, socioeconomic deprivation, etc).<sup>20–21</sup>

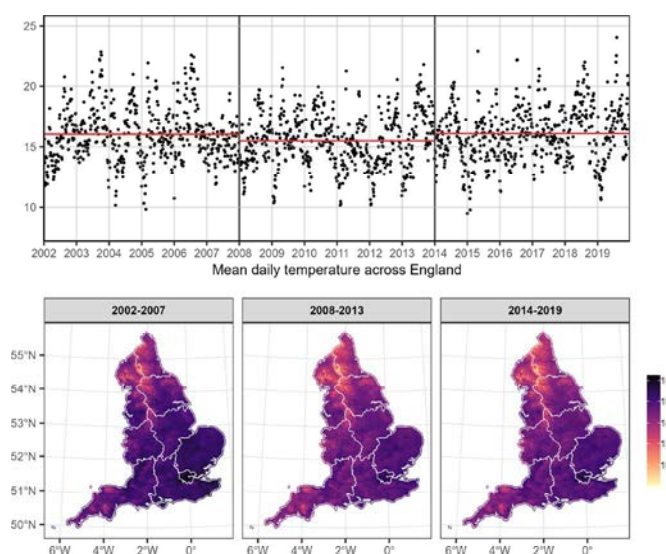
## METHODS

### Study population

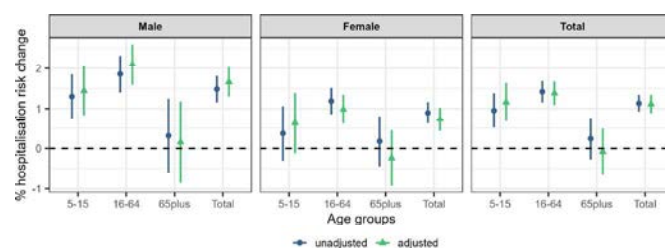
We retrieved all inpatient hospital admissions for asthma in England during 2002–2019 from NHS Digital Hospital Episode Statistics data held by the UK Small Area Health Statistics Unit. Age, postcode of residence at time of hospitalisation and date of hospitalisation were available for each record. We investigated the main diagnostic groups J45 (Asthma) and J46 (Status asthmaticus) according to the International Classification of Diseases version 10 as the main diagnosis of the hospitalisation.<sup>22</sup> The analysis is restricted to June, July and August during which the highest temperatures are reached in England. Because of considerations related with the diagnostic uncertainty and miscoding of asthma in young children,<sup>23</sup> we excluded the 0–4 age group from our analysis.

### Exposure

Daily temperatures at 1 km×1 km resolution were available from the UK Met Office and obtained with methods described elsewhere.<sup>24</sup>



**Figure 1** Top panel: mean of the mean daily temperature (°C) during summer months across England between 2002 and 2019. The red lines show the mean across the different periods (2002–2007, 2008–2013 and 2014–2019). Bottom panel: mean of the mean daily summer temperature (°C) across the 1 km×1 km grid by period. The grey areas define the regions in England.



**Figure 2** Median percentage asthma hospitalisation risk for every 1°C increase in the daily mean summer temperature and 95% credible intervals by sex and age for the unadjusted and fully adjusted (precipitation, relative humidity, wind speed, national holidays and recurrent hospitalisations) models.

In brief, the daily temperature in each grid is estimated based on inverse distance weighted interpolation of monitoring data, also accounting for latitude and longitude, elevation, coastal influence and proportion of urban land use. We calculated mean daily temperature taking the average of maximum daily and minimum daily temperatures during 2002–2009. We selected the mean as the metric to capture the average daily exposure to temperature, in contrast with the min, which reflects exposure at night, or the max, which reflects exposure at midday. To assign daily mean temperature to health records, the postcode centroids of each patient were spatially linked to the 1 km×1 km grid cell, applying a 100 m fuzziness to the postcode location to fulfil governance requirements.<sup>20</sup> For the main analysis, we averaged the daily mean temperatures across the 3 days prior to the hospital admission (lags 0–3), as the delayed effect of heat exposure on health outcomes is expected to last a few days.<sup>15–20–25</sup>

### Confounders

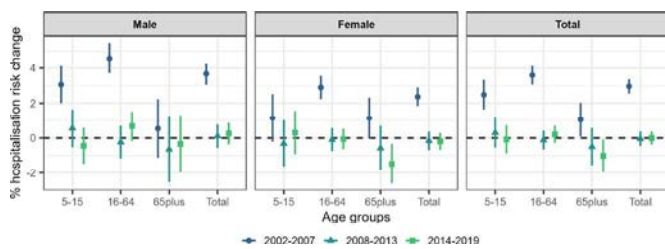
Our main assumptions about possible confounders are shown on the directed acyclic graph (DAG) in online supplemental figure S1. Notice that confounders accounted for through the study design, for instance, deprivation, are omitted from the DAG. Based on the DAG, we decided to account for meteorology (relative humidity, precipitation and wind speed) and national holidays, whereas we assumed that air pollution species (eg, NO<sub>2</sub>, PM<sub>2.5</sub>, PM<sub>10</sub> and O<sub>3</sub>) and grass pollen are more likely to mediate, rather than confound, the relationship between temperature and asthma hospitalisation risk.<sup>26</sup> Mean daily precipitation (mm) at 1 km×1 km resolution between 2002 and 2019 was retrieved from the UK Met Office.<sup>24</sup> Wind speed and relative humidity were retrieved from the UERRA regional reanalysis for Europe and were available daily at 11 km×11 km spatial resolution.<sup>27</sup> National holidays were defined as a binary variable, 0 being a holiday and 1 otherwise. We accounted for national holidays as hospital admission rates are different during a national holiday and at the same time exposure to temperature might be greater as more people are outdoors.<sup>28</sup>

### Effect modification

We examined effect modification by age group, sex (males, females), period (2002–2007, 2008–2013 and 2014–2019) and space (nine regions in England, online supplemental figure S2). The subgroup analysis by age group was done for children (5–15), working age adults (16–64) and older adults (65+), selected for consistency with previous studies.<sup>15–17</sup>

### Statistical methods

We used a time-stratified case–crossover design, commonly used for analysing the effect of transient exposures.<sup>29–31</sup> The temperature on the day of the asthma hospitalisation (event day) is compared with the temperature on non-event days. Within this design, each case acts as its own control, controlling for individual-level factors that do not vary over time (eg, age, sex and ethnicity) or vary slowly (eg, deprivation). We selected non-event days on the same day of the week, calendar month and year as the event day



**Figure 3** Median percentage asthma hospitalisation risk for every 1°C increase in the daily mean summer temperature and 95% credible intervals by sex, age and period (2002–2007, 2008–2013 and 2014–2019) for the fully adjusted (precipitation, relative humidity, wind speed, national holidays and recurrent hospitalisations) models.

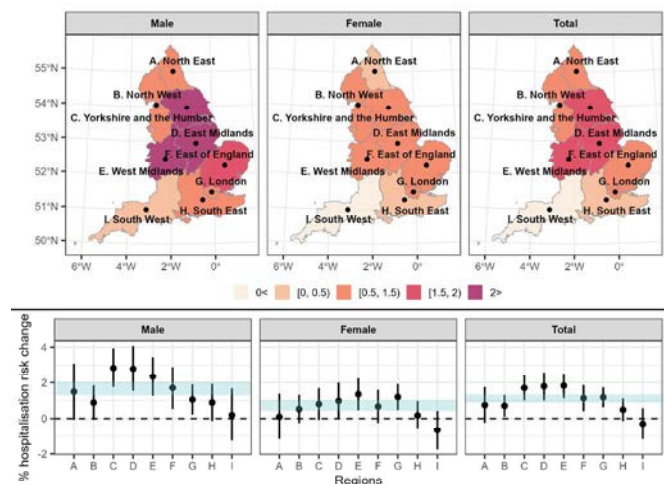
to avoid overlap bias,<sup>32</sup> which also accounts for seasonality (within summer) and long-term trends.<sup>33</sup>

We specified Bayesian hierarchical conditional Poisson models, with a fixed effect on the event/non-event day grouping.<sup>33 34</sup> The above specification offers an alternative to the conditional logistic model allowing for more flexibility and reducing the computational burden.<sup>34</sup> We accounted for patient clustering due to recurrent hospitalisations using a parameter term per patient with exacerbation history, specified as a realisation from a normal distribution with zero mean and common variance. To investigate effect modification, we repeated this analysis by age, sex, period and region.

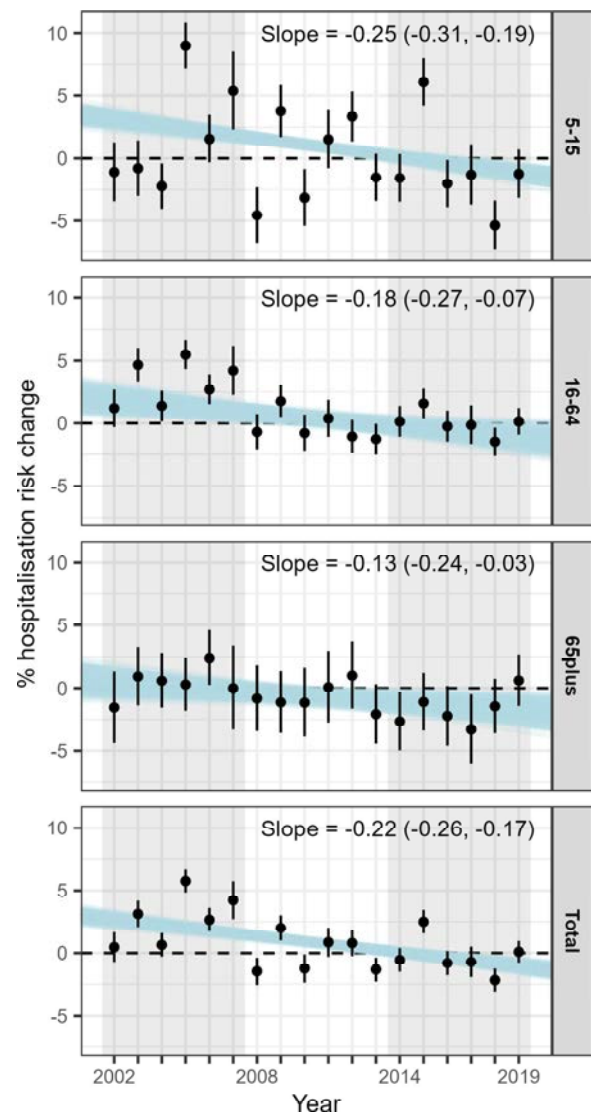
### Sensitivity analyses

As the effect of temperature on health is typically non-linear,<sup>20 25</sup> we investigated departures from the linearity assumption. To do so, we modelled temperature using a random walk of order 2, a Gaussian process over the temperature domain with zero mean and covariance that depends on the two previous and two subsequent observations.<sup>35</sup> We also examined sensitivity with respect to the lag choice, focusing on any lag between 0 and 5.

All results are reported as medians and 95% credible intervals (CrI; 95% probability that the true values lie within this interval) of % increase in hospitalisation risk for every 1°C increase in temperature across the unadjusted and fully adjusted (for rainfall, relative humidity, wind speed and national holidays) models. All analyses are run in Integrated Nested Laplace Approximation.<sup>36</sup> The code



**Figure 4** Top panel: median percentage asthma hospitalisation risk for every 1°C increase in the daily mean summer temperature by sex and region based on the fully adjusted (precipitation, relative humidity, wind speed, national holidays and recurrent hospitalisations) models. Bottom panel: median percentage asthma hospitalisation risk for every 1°C increase in the daily mean summer temperature and 95% credible intervals (CrI) by region based on the fully adjusted (precipitation, relative humidity, wind speed, national holidays and recurrent hospitalisations) models. The shaded area illustrates the 95% CrI of the asthma hospitalisation risk nationwide by sex (fully adjusted models).



**Figure 5** Median percentage asthma hospitalisation risk for every 1°C increase in the daily mean summer temperature and 95% credible intervals by age and year for the fully adjusted (precipitation, relative humidity, wind speed, national holidays and recurrent hospitalisations) models. The blue lines reflect the uncertainty of linear temporal trend of the effect. The text annotation gives the median of the slopes together with the 95% credible intervals. The grey shading on the background defines the three periods (2002–2007, 2008–2013, 2014–2019).

for running the analysis is available online at [https://github.com/gkonstantinou/asthma\\_temperature](https://github.com/gkonstantinou/asthma_temperature).

### Post hoc analysis

In a post hoc analysis we examined how the effect of temperature varies by year. We first fitted the fully adjusted model for each age group and year separately. We then drew 1000 from the posteriors of the effect of temperature for each age group and year and fitted 1000 linear models by age group to examine the temporal trend of the temperature effect.

## RESULTS

### Population

We retrieved 1 268 725 records with a hospital admission for asthma during 2002–2019 in England. After removing 6116 duplicate records, 12 records with place of residence outside England, 1 002 512 that did not occur during summer months, 34 605 aged <5 years and 180 records with missing sex or age, we had 260 085 records available for the analysis (online supplemental figure S3). Most of the admissions occurred for people between 16 and 64 years old ( $n=135\,011$ ) and females ( $n=81\,336$ ) (online supplemental table S1).

## Exposure

Figure 1 shows the mean of the mean daily temperature across all 1 km×1 km grid cells (top panel) and across the summer months by period (2002–2007, 2008–2013 and 2014–2019) in England. The maximum mean daily temperature across England is 24.1°C and was observed in 2019 (top panel, figure 1). The mean of the mean daily temperature across England was 16.0°C during 2002–2007, 15.5°C during 2008–2013 and 16.1°C during 2014–2019 (red lines, top panel, figure 1). The mean of the mean daily temperature across the summer months varied from 8.9°C to 18.5°C during 2002–2007, from 8.1°C to 17.5°C during 2008–2013 and from 8.0°C to 17.8°C during 2014–2019 (bottom panel, figure 1).

## Age and sex effect modification

Figure 2 shows the % change in hospitalisation risk for every 1°C increase in the ambient summer temperature for the different age and sex subgroups during 2002–2019 across the unadjusted and the adjusted models. Accounting for rainfall, relative humidity, wind speed and national holidays does not seem to affect much the observed relationship (figure 2). Overall, we found a 1.13% (0.92% to 1.34%) and 1.11% (0.88% to 1.34%) increase in the risk of hospital admission for every 1°C increase in the ambient summer temperature in the unadjusted and adjusted models, respectively (online supplemental table S2). The effect is consistently higher for males and there is weak, if any, evidence of an effect of temperature for people aged 65 or older. The highest effect was observed for males aged 16–64 with a 1.86% (1.40% to 2.32%) and 2.10% (1.59% to 2.61%) increase in the hospitalisation risk in the unadjusted and adjusted models (figure 2 and online supplemental table S2).

## Temporal effect modification

We examined temporal vulnerabilities of asthma hospitalisation to temperature during summer months. Using the adjusted models, we observe an association of temperature with asthma hospitalisation during 2002–2007, with a 2.96% (2.56% to 337%) increase in hospitalisation risk per 1°C increase in temperature, whereas there is inconclusive evidence for the periods 2008–2013 (–0.04%; –0.46% to 0.37%) and 2014–2019 (–0.01%; –0.39% to 0.37%) (figure 3 and online supplemental table S2). The total effect in figure 2 seems to be mainly driven by males, 16–64 years old, during 2002–2007, with a 4.58% (3.71%, 5.46%) increase in the hospitalisation risk for every 1°C increase in temperature (figure 3 and online supplemental table S3). For the rest of the age and sex groups assessed by period the evidence is weaker (figure 3 and online supplemental table S2).

## Spatial effect modification

Figure 4 presents the spatial vulnerabilities by region and by sex in the adjusted models. We observe that males in Yorkshire and the Humber and East and West Midlands are the most vulnerable with a % increase in hospitalisation risk being larger than 2% per 1°C increase in temperature in the adjusted models (figure 4). Populations in the South West are consistently the least vulnerable (figure 4).

## Sensitivity analyses

Allowing for flexible fits using random walk of order 2 to model temperature validated our linearity assumption in general (online supplemental figure S4). The subgroup deviating from linearity is females between 15 and 65, suggesting an effect most prominent for temperatures higher than 20°C (online supplemental figure S4). When we examined the different lags we found that the lags contributing most to the effect are 0–3 (online supplemental figure S5).

## Post hoc analysis

The results of the post hoc analysis are shown in figure 5. The 1000 blue lines per age group show an overall decreasing trend on the temperature effect of the years, varying from –0.25 (–0.31, 0.19) in people aged between 5 and 15 years to –0.08 (–0.13, –0.24) in people aged over 65 years (figure 5). For the total age group, the ef-

fect is –0.22 (–0.27, –0.17), suggesting that the percentage asthma hospitalisation risk per 1°C increase in temperature is decreasing by 0.22 for each coming year (figure 5).

## DISCUSSION

In this nationwide study in England investigating the short-term effect of ambient summer temperature on asthma hospitalisations during 2002–2019, we find evidence of an increased risk of asthma hospitalisation associated with increasing temperature. The effect of ambient temperature exposure appears to be modified by sex and age, with males aged between 16 and 64 years being the most vulnerable population. When we assessed the change in magnitude of this effect over time, we found that the temperature-related asthma hospitalisation risk is largest during 2002–2007, whereas there is weak, if any, effect during 2008–2013 and 2014–2019. We also observed some spatial variation with populations living in the regions of Yorkshire and the Humber and East and West Midlands being most vulnerable.

Our study is comparable with previous studies assessing asthma hospital admissions and ambient temperature during warmer months, rather than studies assessing heat waves and extreme temperatures.<sup>8</sup> Our study is in line with a time series study in Hong Kong using lag 0–3 mean temperature and accounting for relative humidity, wind speed, solar radiation, influenza and air pollution, which reported an increased asthma hospitalisation relative risk (1.19; 95% CI 1.06, 1.36) at 30°C compared with 27°C during the hot season.<sup>15</sup> The same study reported that the effect of temperature during the hot season was largest in adults aged between 15 and 59 years.<sup>15</sup> Our results are in contrast with those of a time series study in Shanghai, China, focusing on different temperature metrics and accounting for meteorology and air pollution, which reported no association between asthma hospitalisations and warm temperatures.<sup>10</sup> A case–crossover study in Brazil during 2000–2015 examined temperature variability and asthma hospitalisations and reported a higher effect in people aged 80 or older, with weak evidence of effect modification by sex.<sup>16</sup> In our study, there is weak evidence that people aged 65 or older were vulnerable, while we observed a strong effect modification by sex for temperature-related asthma hospitalisations.

The age modification we observed might have multiple explanations. People aged between 5 and 64 years are likely to be exposed more to environmental triggers in comparison to the older subgroup who stay mostly at home, do not work and have a less active social life. The adult population could also be more vulnerable due to the higher prevalence of smoking in the adult population resulting in a more severe airway inflammation and lower lung function, which potentially could lead to increased vulnerability to higher temperatures.<sup>15, 37</sup> The above suggests engaging patients and carers to raise awareness of the adverse effects of temperature. The weak observed effect in the older population could also reflect outcome misclassification (non-differential) due to the multiple comorbidities that this population is suffering from.

We observed that the effect of ambient temperature on asthma hospitalisations has attenuated over time. Potential explanations of this trend include adaptive mechanisms to heat exposure over time,<sup>21</sup> such as more consistent adherence to medication over time, effectiveness of the heat alerts (they were introduced in 2004), infrastructure changes and improved healthcare. Based on the period analysis, the effect is most prominent in males aged 15–65 years, which could also point towards sex-related differences in exposure due to differences in behaviours, lifestyle and occupation, but also could imply differences in the prevalence of other comorbid chronic diseases, such as chronic obstructive pulmonary disease.<sup>38</sup> Nevertheless, we cannot rule out potential residual confounding due to data availability or due to differences in the exposure (duration of heat period, changes in maximum/minimum temperatures) across the years. The decreasing trend should be further monitored and re-examined in the future considering future changes in the climate, factors influenced by these changes (eg, allergen concentration) and the increasing burden of asthma.

In line with our study, previous studies in Taiwan and Brazil have reported effect modification by space.<sup>11–16</sup> We observed that populations in the regions of Yorkshire and the Humber and East Midlands are the most vulnerable. Potential explanations include spatial effect modifiers that are most prominent in these regions, such as allergen concentration, higher air pollution levels (particulate matter) and higher prevalence of smoking. Nevertheless, we should iterate that the evidence for heterogeneity in the effect by space is weak as the CrIs of the effects overlap with the CrIs of the effects nationwide.

The observed discrepancies with some previous studies can have multiple explanations. The choice of confounding adjustment can impact the results. In addition, the temperature metrics and lags used across the studies are not consistent. Apart from min, mean, max and range of temperature, a couple of studies have used temperature variation.<sup>16–39</sup> In our study we used the mean, as we were interested in the overall effect of the temperature during the day and were not interested in the impact of night temperatures (using min) or extreme heat during midday (using max). It is hard, nevertheless, to predict how this choice could impact the results, as the different temperature metrics point towards different exposure windows. Previous studies had available coarser geographical resolution (city or county level), which can lead to misclassification of the exposure and inadequate confounding adjustment. In addition, most previous studies are focused on urban settings,<sup>9–12–15–17</sup> whereas our study provides nationwide estimates. Last, resources for healthcare setting, health promotion and infrastructure across the different countries could contribute to the observed discrepancies.

The main strength of our study is the availability of high geographical resolution of the outcome. This allows us to link the outcome with the exposure and confounders with very high precision minimising potential misclassification. As hospitalisations were retrieved from NHS Digital (nationwide central data on hospital admissions), we expect to cover most of the asthma hospitalisation burden in England, minimising any selection bias. We used individual-level data, which allows us to examine individual-level vulnerabilities, for example, related to age and sex, and to avoid ecological bias.

We assigned temperature exposure using the residential address of the cases and used this as a proxy for individual exposure to temperature. This proxy is expected to be more accurate for adults aged 65 years or older who are expected to stay longer at home or somewhere in the direct proximity. In addition to this, we used the outdoor temperature which is expected to be different from the temperature inside the house. The misclassification induced by this is not expected to be differential and to lead to bias. Data for relative humidity and wind speed were only available at coarse geographical resolution, namely at 11 km×11 km, which likely misses the localised trends in these covariates and could potentially lead to inadequate adjustment for confounding. The results depend on the assumption that air pollution is a mediator and not a confounder. We could not check the validity of this assumption, as data for air pollution are available only after 2008, when the effect of temperature on asthma hospital admissions is weak.

The direct biological mechanism by which higher temperatures trigger asthma exacerbations is unclear. Warm temperatures can aggravate the respiratory system-related burden, as they can affect the electrolyte balance.<sup>40</sup> High temperatures may activate the c-fibre nerve and enhance bronchoconstriction leading to higher morbidity.<sup>15</sup> In addition, warmer temperatures can increase allergen or air pollution (in particular O<sub>3</sub>) concentrations, or help the reproduction and spread of viruses and bacteria causing or aggravating respiratory diseases.<sup>15</sup>

This study provides evidence of an association between warm temperatures and asthma exacerbations in England. More studies in counties with different climate, healthcare and social behaviours are needed to further understand the generalisability of the results. The effect of warm temperatures on asthma hospitalisation has attenuated over time suggesting potential adaptive mechanisms

to heat exposure or differences in behaviours, lifestyle, comorbid conditions, other environmental exposures and occupation over time.

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# O conjunto de resultados fundamentais para a reabilitação de pacientes com DPOC: resultados de um inquérito Delphi modificado

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## RESUMO

**Introdução** Existe uma elevada heterogeneidade de resultados e medidas reportadas nos ensaios de reabilitação pulmonar (RP) de pessoas com doença pulmonar obstrutiva crónica (DPOC). Isto prejudica a comparabilidade e a avaliação comparativa dos estudos de RP. Desenvolvemos um conjunto de resultados fundamentais (CRF) para suplantarmos estes desafios.

**Métodos** Este estudo foi informado por uma revisão sistemática e por dois estudos qualitativos e teve a participação dos pacientes desde o início. Foi disponibilizado um inquérito de Delphi de duas rondas em sete línguas. Os resultados (n=63) avaliados como 7–9 (crucial) por ≥70 % dos participantes e 1–3 (não tão importante) por ≤15 % dos participantes de ambos os grupos na escala de Likert foram automaticamente incluídos no CRF, ao passo que os resultados que foram considerados cruciais por apenas um dos grupos foram posteriormente debatidos pelos autores numa reunião.

**Resultados** Um total de 299 pessoas (n=229 profissionais de saúde/investigadores/decisores políticos; n=70 pessoas com DPOC e cuidadores informais) participaram no estudo (83 % retenção), que abarcou 29 países em cinco continentes. Depois da segunda ronda, foram incluídos seis resultados, aos quais se somaram três em reunião. O CRF final inclui dispneia, cansaço, capacidade de exercício funcional, qualidade de vida relacionada com a saúde, comportamentos de saúde/estilo de vida, conhecimentos sobre a doença, função dos músculos dos membros inferiores, objetivos pessoais e atividades problemáticas da vida quotidiana.

**Conclusão** Um CRF para RP de pessoas com DPOC está agora disponível e pode ser usado por diferentes intervenientes para melhorar a consistência e a comparabilidade dos estudos, avaliar comparativamente a RP e melhorar a qualidade dos cuidados oferecidos. Os estudos futuros devem estabelecer as medidas principais e investigar a utilização deste CRF.

## INTRODUCTION

Pulmonary rehabilitation (PR) is recognised as an essential pillar of the management of symptomatic patients with chronic obstructive pulmonary disease (COPD).<sup>1,2</sup> Generally, PR programmes are safe and have a positive impact on patients' daily symptoms, exercise capacity and quality of life.<sup>2</sup> Nevertheless, a systematic review identified high heterogeneity in the measurement of outcomes in PR trials.<sup>3</sup> This hinders the comparison of programmes, effective evidence synthesis (ie, meta-analysis)<sup>4</sup> and limits benchmarking of PR.<sup>5</sup>

Due to the widely recognised need to tackle this heterogeneity and to establish metrics demonstrating the quality of PR, some outcome indicators have been proposed.<sup>1,5–11</sup> Such initiatives have, however, been exclusively based on expert opinions, with no robust methodology such as the development of a core outcome set (COS) followed.

A COS is defined as an agreed standardised set of outcomes that should be measured and reported, as a minimum, in all clinical trials in specific areas of health or healthcare.<sup>4</sup>

## Key messages

### What is already known on this topic

► Pulmonary rehabilitation is an effective intervention for people with chronic obstructive pulmonary disease (COPD). However, the literature shows high heterogeneity of outcomes and measures reported in pulmonary rehabilitation trials. This hinders evidence synthesis and benchmarking of the intervention.

### What this study adds

► Through a multistakeholder consensus process, this study defined a core outcome set for pulmonary rehabilitation of people with COPD. The core outcome set consists of nine outcomes that should be measured before and after every pulmonary rehabilitation programme.

### How this study might affect research, practice or policy

► Use of this core outcome set might increase consistency among trials and thus the capacity to meta-analyse data, lessen outcome reporting bias, help to benchmark pulmonary rehabilitation and improve the quality of programmes through quality control assessments, increase transparency to payers and provide a structured assessment guide for clinicians.

A COS for PR has the potential to generate significant clinical and research impacts. A COS can aid the assessment of the quality of PR programmes in clinical practice, which may lead to improvements in the quality of care provided. Second, by establishing a common set of outcomes to be measured, a COS can also facilitate the comparison and synthesis of study results, which could inform future research and clinical practice.

Hence, this study aimed to define a COS that should be consistently measured and reported in PR of people with COPD.

## METHODS

This study consisted of a two-round Delphi survey followed by a meeting among authors to finalise the COS. The study is part of a COS registered in the Core Outcome Measures in Effectiveness Trials (COMET) initiative database (<https://www.comet-initiative.org/Studies/Details/1151>). The COS was developed considering the COS-STAndards for development recommendations<sup>12</sup> and the COMET handbook,<sup>13</sup> and is reported according to the COS-STAndards for Reporting Statement.<sup>14</sup>

This study had patient and public involvement<sup>13 15</sup> since its inception, through the inclusion of a patient representative in the design and development of the study. The patient representative ensured that the process was patient-friendly, for example, length of questionnaire and language suited for patients, and that the study had sufficient patient input.<sup>16</sup>

### Participants and inclusion/exclusion criteria

Two panels of experts were constituted: people with COPD and informal caregivers, and healthcare professionals, researchers and policy-makers.

People from different countries and backgrounds were recruited, to ensure diverse contributions and international applicability.<sup>17</sup> Although there is no consensus on the most suitable sample size for Delphi surveys, a minimum of 10–18 participants per stakeholder group has been suggested.<sup>18</sup>

Patients and informal carers were recruited through the research team's network, and patient associations (48 were contacted). Healthcare professionals, researchers and policy-makers were recruited via the teams' network, and professional societies/associations (21 were contacted). The study was also disseminated on social media and among those previously involved in a qualitative study<sup>19</sup> to maximise the recruitment.

Inclusion and exclusion criteria were explicitly stated by email and provided with the social media dissemination material. Patients were included if they were adults, diagnosed with COPD and had participated or were participating in a PR programme. Informal carers were included if they were adults, had an informal relationship with a person with COPD (eg, family, friend, neighbour) and had provided support (eg, physical, practical, psychosocial, financial) to a person with COPD while they were included in a PR programme. Healthcare professionals, researchers and policy-makers were included if they had been involved in the design, implementation, assessment of PR or data resulting from it. Participants were excluded if they had an impairment in communication (reading and/or understanding).

### Information sources

The initial list of outcomes was developed by combining the outcomes retrieved from a systematic review<sup>3</sup> and those obtained by interviews with patients, informal carers, and healthcare professionals, researchers and policy-makers in two other studies.<sup>19 20</sup> Due to the large number of outcomes (163 from systematic review and eight from qualitative studies), some outcomes with similar health meanings (eg, walking distance and cycling time) were collapsed into broader outcomes (eg, exercise capacity). This approach was chosen as Delphi studies with higher number of items and larger panels are associated with lower response rates.<sup>21</sup> The final list of the first round of the survey was composed of 57 out-

comes with descriptors that were discussed and agreed by the research team (please see online supplemental appendix A).

### The survey

The Delphi survey was available electronically and in paper for local (Portuguese) participants who wanted to participate but could not access the online survey (, digital skills). The survey was developed using Qualtrics (Qualtrics XM, Provo, Utah, USA).

To maximise the possibility of developing a global COS, the survey was translated from English into Portuguese, Dutch, Spanish, Italian, French and German, using forward translation with one proficient speaker of English and each other language.<sup>22</sup>

The Delphi survey was pilot tested with a patient representative and a healthcare professional, to ensure its length was feasible and that it was easy to understand.

The initial part of the survey was composed of a brief explanation of the research, a video developed by the COMET initiative to explain the development of a COS,<sup>23</sup> advantages and disadvantages of taking part in the study, a plain language summary<sup>24</sup> and the informed consent. A document with a plain language description and a representative image (when possible) for each outcome that was reviewed by two healthcare professionals/researchers and a patient representative,<sup>13</sup> was also provided (online supplemental appendix B).

Participants were asked to provide information regarding their sex, age, occupation, country and stakeholder group. Informal caregivers were also asked to disclose the type of relationship with the patient (eg, family member).

The list of outcomes was alphabetically ordered to avoid bias.<sup>25</sup> Participants scored each outcome in a 9-point Likert scale in which the outcomes scored from one to three were 'not that important', 4–6 were 'important but not critical' and 7–9 were 'critical' to measure.<sup>26</sup> An option of 'unable to score' was also provided, as some participants might have never experienced a particular outcome.<sup>16</sup> At the end of the first round of the survey, participants were able to suggest outcomes to be scored on the following round to ensure all outcomes valuable for these stakeholders were considered.<sup>27</sup>

The second round of the survey used the same scoring system and contained all outcomes of the previous round and the additional ones suggested by participants (online supplemental appendix A). Feedback of the previous round with the score distribution of each stakeholder group for each outcome was provided (online supplemental appendix C), as confrontation with the opinions of other participants could increase consensus.<sup>27</sup> Three rounds of gentle reminders were sent by email, asking participants to complete the second round of the survey to minimise high attrition rates.<sup>27</sup>

After the second round, outcomes that were scored between 7 and 9 by  $\geq 70\%$  of the participants and between 1 and 3 by  $\leq 15\%$  participants from both groups were automatically included in the final COS, outcomes that only one of the groups considered essen-

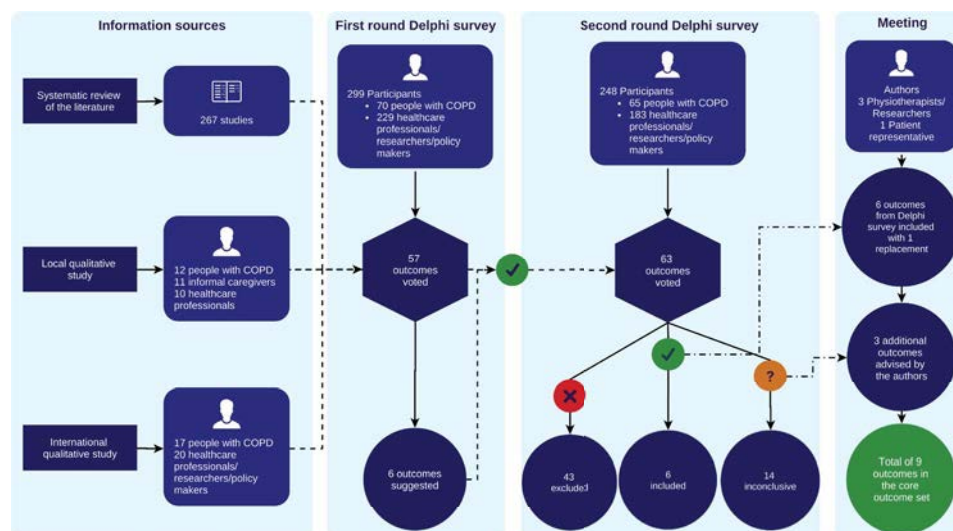
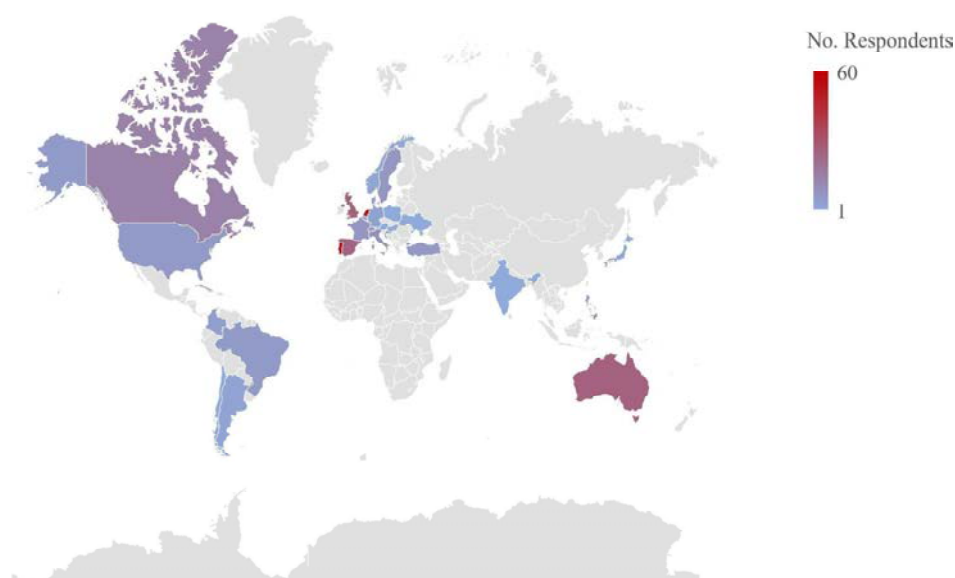


Figure 1 Flow diagram of the study process. COPD, chronic obstructive pulmonary disease.



**Figure 2** Distribution of responses to the first round of the Delphi survey (n=299), across the 29 countries that participated.

tial were further discussed among authors in a meeting, and the remaining outcomes were excluded from the COS.<sup>17</sup>

All analyses were performed using R (V.4.1.2, R Foundation for Statistical Computing, Vienna, Austria) and Excel (Microsoft, Redmond, Washington, USA).

### Meeting to finalise the COS

The meeting consisted of a group discussion, followed by voting of uncertain outcomes by the four authors.<sup>13</sup> It was not possible to

conduct a standard consensus meeting with participants from the Delphi, due to lack of funding and human resources (eg, live translation for participants needed due to language barriers) and time constraints (eg, scheduling a meeting with 10–20 people from different time zones without any incentive). The first author is a 31-year-old woman, who is a physiotherapist and a PhD holder, with 7 years of experience working with PR and people with COPD. AM is a 45-year-old female and MAS is a 47-year-old male, both physiotherapists, PhD holders and researchers with more than 20

**Table 1** Percentage of participants scoring the outcome as crucial, with list of outcomes voted as crucial by both stakeholder groups (included), and only by one of the stakeholder groups (uncertain), across Delphi rounds

|                                                         | First round                                     |                                          | Second round                                    |                                          |
|---------------------------------------------------------|-------------------------------------------------|------------------------------------------|-------------------------------------------------|------------------------------------------|
|                                                         | People with COPD and informal caregivers (n=70) | HCPs, researchers, policy-makers (n=229) | People with COPD and informal caregivers (n=65) | HCPs, researchers, policy-makers (n=183) |
| Outcomes voted as crucial by both groups                |                                                 |                                          |                                                 |                                          |
| Dyspnoea                                                | 84.5%                                           | 95.7%                                    | 83.1%                                           | 96.2%                                    |
| Exercise capacity                                       | 76.1%                                           | 86.1%                                    | 84.6%                                           | 92.9%                                    |
| Fatigue                                                 | 69.0%                                           | 77.0%                                    | 70.8%                                           | 81.4%                                    |
| Muscle function                                         | 60.6%                                           | 72.2%                                    | 76.9%                                           | 76.0%                                    |
| Health-related quality of life                          | 81.7%                                           | 88.3%                                    | 75.4%                                           | 94.5%                                    |
| Impact of the disease                                   | 76.1%                                           | 81.7%                                    | 76.9%                                           | 80.9%                                    |
| Outcomes only voted as crucial by one stakeholder group |                                                 |                                          |                                                 |                                          |
| Acute exacerbations of COPD                             | 54.9%                                           | 80.4%                                    | 58.5%                                           | <b>86.3%</b>                             |
| Coping strategies                                       | 63.4%                                           | 73.5%                                    | 56.9                                            | <b>82.5%</b>                             |
| Energy expenditure                                      | 67.6%                                           | 53.9%                                    | <b>78.5%</b>                                    | 53.0%                                    |
| General well-being                                      | 70.4%                                           | 72.2%                                    | 69.2%                                           | <b>81.4%</b>                             |
| Lung function                                           | 85.9%                                           | 43.9%                                    | <b>80.0%</b>                                    | 21.9%                                    |
| Respiratory muscle function                             | 78.9%                                           | 47.4%                                    | <b>73.8%</b>                                    | 32.8%                                    |
| Achieving personal goals                                | 54.9%                                           | 77.8%                                    | 41.5%                                           | <b>82.5%</b>                             |
| Activities of daily living                              | 63.4%                                           | 89.1%                                    | 67.7%                                           | <b>89.1%</b>                             |
| Health behaviours/lifestyle                             | 67.6%                                           | 74.3%                                    | 56.9%                                           | <b>80.9%</b>                             |
| Knowledge about the disease                             | 70.4%                                           | 69.1%                                    | 58.5%                                           | <b>78.7%</b>                             |
| Motivation to exercise/be physically active             | 67.6%                                           | 83.5%                                    | 66.2%                                           | <b>87.4%</b>                             |
| Physical (in)activity                                   | 62.0%                                           | 82.2%                                    | 60.0%                                           | <b>88.5%</b>                             |
| Self-management                                         | 62.0%                                           | 76.1%                                    | 60.0%                                           | <b>83.1%</b>                             |
| Smoking cessation                                       | 54.9%                                           | 82.2%                                    | 60.0%                                           | <b>86.9%</b>                             |

Percentages represent the frequencies of participants that voted the outcome as crucial. Bold font indicates meeting the threshold for inclusion ( $\geq 70\%$  of participants voted outcome as crucial).

COPD, chronic obstructive pulmonary disease; HCP, healthcare professionals.



**Figure 3** Core outcomes included in the core outcome set using the domains (physiological/clinal outcomes, life impact outcomes) of the Core Outcome Measures in Effectiveness trials initiative’s taxonomy. Outcomes with the symbol checked at green are those recommended by several stakeholders of the Delphi process, and outcomes with a semichecked orange mark represent outcomes advised by authors that should be further researched.

years of experience in the field, namely conducting COS and developing PR-related policy documents. IS is a female patient with COPD with vast experience in integrating research as a former European Lung Foundation President and current President of the Portuguese Association of People with COPD and Other Respiratory Diseases.

Prior to the meeting, handouts were sent by SS-M to the remaining authors as suggested by the COMET initiative,<sup>28</sup> consisting of (1) an introduction of what is a COS, information about what happened in the project before, (2) a plan for the meeting and (3) the list of outcomes that were agreed previously; the list of outcomes that were excluded; and the list of outcomes that needed a decision during the meeting with a plain language definition and an image.

The meeting was then conducted online, through Zoom (California, USA). A nominal group technique was used to ensure all participants’ thoughts were considered.<sup>29</sup> The session started with an introductory phase where there was a slide set prepared by the moderator (SS-M) to explain the results of the Delphi survey and to structure the meeting.

Outcomes from the Delphi survey that were automatically included were first reviewed, to finalise the recommendations and make possible adjustments. Then, for inconclusive outcomes, a silent generation of ideas was performed. Participants were asked to think and write which of those outcomes (if any) should be in the final COS and why, without consulting other people.<sup>29</sup> Participants were invited to share their ideas to the group, one at a time.<sup>29</sup> A discussion was then followed with pros and cons of including each outcome.<sup>29</sup> Finally, electronic voting consisted of asking participants at the same time whether each outcome mentioned in the previous phase was or was not crucial to assess the effectiveness of PR. They were asked to keep in mind that a maximum of 9 outcomes would be considered, to ensure the applicability of the COS.<sup>17</sup> Voting among authors (n=4) was considered consensual if nobody or just one person disagreed (25% threshold).

RESULTS

The Delphi survey was composed of two rounds.<sup>13</sup> The first round occurred from 17 May 2022 to 8 July 2022 and the second from 21 September 2022 to 31 October 2022. The meeting to finalise the COS took place on the 12 January 2023 and lasted 63 min. A flow diagram of the study process can be observed in figure 1.

Nine of the 48 patient associations contacted responded to the survey and 8 of the 21 professional organisations engaged with the survey. A total of 299 participants from 29 countries completed the first round of the survey, of whom 198 were healthcare professionals, 103 were researchers, 67 were people with COPD, 10 were policy-makers and 3 were informal caregivers. Participants were mostly females (n=176, 58.9%) with an average age of 49 (±14) years old. Of all healthcare professionals, most respondents were physiotherapists (n=98, 49.2%) or medical doctors (n=49, 24.6%). A retention rate of 82.9% was achieved in the second round, with 27 countries involved. Characteristics of the sample are displayed in online supplemental appendix D, and a map of the distribution of responses can be observed in figure 2.

Opinions were consistent between rounds with a change in voting for four outcomes (energy expenditure, fatigue, general well-

| Table 2 Outcome definitions for the core outcomes, based on available literature and authors’ consensus |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|---------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Outcome                                                                                                 | Definition                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Dyspnoea                                                                                                | Dyspnoea has been described as a ‘subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity’. <sup>52</sup>                                                                                                                                                                                                                                                                                                         |
| Fatigue                                                                                                 | Fatigue can be defined as ‘a subjective, unpleasant symptom which incorporates total body feelings ranging from tiredness to exhaustion creating an unrelenting overall condition which interferes with individuals’ ability to function to their normal capacity’. <sup>53</sup>                                                                                                                                                                                                 |
| Functional exercise capacity                                                                            | Exercise capacity, and specifically functional exercise capacity can be defined as ‘one’s maximal potential to realise a functional activity in a standardised environment (eg, walking distance during the 6-minute-walk test)’. <sup>54</sup>                                                                                                                                                                                                                                   |
| Health-related behaviours/lifestyle                                                                     | Health-related behaviours can be defined as ‘actions taken by individuals that affect health or mortality. These actions may be intentional or unintentional, and can promote or detract from the health of the actor or others’. <sup>55</sup> There are multiple behaviours that are related to lifestyle choices which impact patients health, such as smoking, physical activity and sleep. <sup>55</sup>                                                                     |
| Health-related quality of life                                                                          | Health-related quality of life refers to the ‘aspects of self-perceived well-being that are related to or affected by the presence of disease or treatment’ <sup>56</sup> or ‘a component of the broader concept of quality of life that is defined as satisfaction with health’. <sup>2</sup>                                                                                                                                                                                    |
| Knowledge about the disease                                                                             | The definition of health literacy used by the WHO was adapted for this outcome that is, the ability of individuals to gain access to, understand and use information about the disease in ways which promote and maintain good health’. <sup>57 58</sup>                                                                                                                                                                                                                          |
| Lower limb muscle function                                                                              | Muscle dysfunction is defined as ‘the loss of at least one of the two main muscle properties: strength and endurance’. <sup>59 60</sup> Although muscle endurance and other properties might be important to assess, <sup>61</sup> it was consensual that lower limb muscle strength should be the core outcome assessed, as it is the most studied muscle characteristic in COPD, has a clear prognostic value, can be improved with PR and is easily measured. <sup>59 62</sup> |
| Personal goals                                                                                          | Personal goals were defined as goals that patients aim to achieve with PR and are set by themselves.                                                                                                                                                                                                                                                                                                                                                                              |
| Problematic activities of daily living                                                                  | Activities of daily living are meaningful tasks of everyday life that can be basic (eg, eating, dressing, bathing) or instrumental that is, associated with independent living (eg, transportation, shopping, managing money, housework). <sup>63 64</sup>                                                                                                                                                                                                                        |

COPD, chronic obstructive pulmonary disease; PR, pulmonary rehabilitation.

being and muscle function). After the first round, 5 outcomes were crucial for both stakeholder groups (dyspnoea, exercise capacity, general well-being, health-related quality of life (HRQoL) and impact of the disease), 14 outcomes were inconclusive (only 1 of the stakeholder groups had at least 70% of people voting as crucial) and the remaining (n=38) would be excluded if the Delphi survey ended. A total of 63 outcomes were voted in the second round, 57 retrieved from the previous studies and 6 suggested by participants in the first round (online supplemental appendix A). After the last round of the survey, 6 outcomes were included in the COS (dyspnoea, exercise capacity, fatigue, HRQoL, impact of the disease and muscle function), 43 were excluded and 14 were further discussed in the meeting. Table 1 shows outcomes that were consensually included after the second round for both groups, and those that were not consensual between groups and were therefore voted in a meeting.

The full process of outcome inclusion and exclusion can be observed in online supplemental appendix D. Outcomes were grouped using the COMET initiative taxonomy.<sup>30</sup>

During the meeting, we decided to rephrase the outcome 'impact of the disease' into 'problematic activities of daily living' and consequently remove 'activities of daily living' from the uncertain outcomes to be voted. This decision was reached due to the similar inherent meaning of the two outcomes (ie, how/which daily activities of patients are affected), and as it was consensual that symptoms and HRQoL (outcomes already included in the COS) already included the measurement of the impact of the disease. Seven of the 13 outcomes that needed a decision were mentioned as important during the nominal group technique and were, therefore, voted: smoking cessation (25% voted to include), lung function (25% voted to include), knowledge about the disease (100% voted to include), coping strategies (25% voted to include), personal goals (100% voted to include), self-management (25% voted to include) and health behaviours/lifestyle (75% voted to include).

The meeting resulted in a recommendation to measure nine outcomes before and immediately after PR programmes. The decision to measure the core outcomes only on a short-term was based on the high heterogeneity of paths patients follow after PR (eg, some patients stop exercising, some engage in physical activity/exercise programmes), which could confound the assessment of PR effectiveness. The final COS is, therefore, composed of the outcomes: dyspnoea, functional exercise capacity, fatigue, health behaviours/lifestyle, HRQoL, knowledge about the disease, lower limb muscle function, personal goals and problematic activities of daily living. Figure 3 shows outcomes that were recommended during the Delphi process and outcomes that are recommended by authors but should be further researched. Definitions for each outcome were determined based on the literature and by consensus of authors during the meeting. These definitions can be used in the future to help choose the measurement instrument for each construct (table 2).

## DISCUSSION

This study developed a COS for PR of patients with COPD. The COS is composed of nine outcomes—dyspnoea, fatigue, functional exercise capacity, health behaviours/lifestyle, HRQoL, knowledge about the disease, lower limb muscle function, personal goals and problematic activities of daily living, which are relevant for various stakeholders.

The proposed set of outcomes is of utmost importance for enhancing both clinical practice and research. From a clinical standpoint, the COS can be an integrated step of an iterative process of improving the quality of PR, such as the Plan-Do-Check/study-Act cycle.<sup>31</sup> Using this four-stage cyclic method, after results are ascertained with the COS, programmes can plan changes, perform them, check whether results were different with the new changes (using the COS) and act towards new steps of improvement if needed. Additionally, the COS can enable comparison of results between patients and centres in clinical practice, promote transparency to payers and can be used as a structured minimal assess-

ment guide. Finally, by demonstrating the benefits of PR in important outcomes, the COS may help to attract funding and influence policy changes.

In terms of research, this COS has various benefits. First, it can increase consistency across trials, leading to a decrease in outcome reporting bias, research waste and an improvement in the ability to conduct meta-analyses. Second, this COS can serve as a vehicle for knowledge translation by enabling comparison of outcomes between COPD and other diseases.

Mental health issues (including symptoms of anxiety and depression) occur frequently in patients with COPD,<sup>32</sup> and PR reduces these symptoms.<sup>33</sup> Therefore, the exclusion of anxiety and depression during the Delphi process was somewhat unexpected. However, this finding is consistent with other outcome measurement recommendations for COPD (PR or physiotherapy-related treatments of COPD, stable and acute states of COPD with no interventions) which did not include mental health outcomes.<sup>11 34–36</sup> Nevertheless, a COS is a minimum of measurements that should be performed. Additionally measuring the effects of PR on mental health is still encouraged, particularly for patients who exhibit these symptoms at baseline.

The Delphi process unveiled substantial variations among stakeholder groups regarding certain outcomes. Lung function and respiratory muscle function were considered crucial outcomes of PR by more than 70% of people with COPD and informal caregivers, but less than 33% of healthcare professionals, researchers and policy-makers voted this outcome as crucial. This is likely due to patients' lack of knowledge of the role of PR in modifying these clinical aspects. Lung function remains unchanged and is not a goal of PR, and inspiratory muscle training seems to have a small effect when provided during PR and just for patients with respiratory muscle weakness.<sup>37 38</sup> In contrast, healthcare professionals, researchers and policy-makers placed greater emphasis on measuring acute exacerbations as an outcome of PR when compared with patients and informal caregivers, which might be explained by their awareness of the significant impact these exacerbations can have on the disease trajectory,<sup>39</sup> and therefore, the need to prevent them. On the other hand, patients may perceive them as sporadic and relatively inconsequential to their long-term health, considering them more as occasional negative experiences. Nevertheless, although some evidence shows PR to be beneficial in preventing re-exacerbations after an exacerbation,<sup>40</sup> its role in preventing them in stable patients is less clear. Overall, these divergent opinions highlight the need to promote COPD and PR-related health literacy, to improve patients' understanding of clinical variables, measurements and what can be expected from PR.

Most outcomes recommended in this COS are not COPD or respiratory-specific (eg, functional exercise capacity, fatigue, health behaviours/lifestyle, HRQoL, personal goals and problematic activities of daily living). In fact, some of these outcomes have also been identified as critical in other COS initiatives such as the International Consortium for Health Outcomes Measurement sets,<sup>41–43</sup> and other rehabilitation-related COS developed for musculoskeletal, cardiac, or neurorehabilitation, and rehabilitation after clinical illness.<sup>44–48</sup> This overlap in outcomes across different conditions and rehabilitation services may facilitate the sharing of resources, comparison of disease trajectories and programmes, enrich knowledge and enable better translation of research findings to other settings.

While this COS provides some key outcome indicators that should be reported, other key indicators for structure and process should also be defined in the future for internal and external quality control purposes.<sup>1 5 49</sup> Structure indicators are related to the infrastructures and resources of PR programmes, such as equipment and personnel available, while process indicators reveal the path of the patient within the service delivered and the elements of care provided (eg, time on waiting list, length and components of programmes).<sup>5 49</sup>

This study has some strengths and limitations. The development of this COS followed a robust methodology recommended by the

COMET initiative<sup>13</sup> and is a result of several studies: a systematic review of 267 studies,<sup>3,2</sup> qualitative studies with 29 patients with COPD, 11 informal carers and 30 healthcare professionals, researchers and policy-makers,<sup>19,20</sup> an international Delphi survey completed by 248 participants (patients and healthcare professionals, researchers and policy-makers) covering<sup>29</sup> countries, and a meeting with three clinicians/researchers and a patient representative. Thus, we believe this COS is valid for different stakeholders and has international applicability. Nonetheless, three of the nine outcomes were chosen only by the authors (impossibility of conducting a larger international meeting due to lack of resources and time availability), although recognised as crucial by one of the stakeholder groups during the Delphi process. These outcomes should, therefore, be further researched, and future studies could confirm their relevance for different stakeholders.

Additionally, we did not characterise participants in great detail and participants' characteristics and beliefs probably contributed to their choices. Therefore, it is possible that some outcomes were not chosen (eg, anxiety) due to the participants characteristics (eg, having no symptoms of anxiety).

A large proportion of countries from Africa and Asia were also not covered in this COS, limiting its applicability in these regions.

This COS is a comprehensive set of outcomes that includes multiple and differential domains, previously acknowledged as needed, due to the complexity of the disease and the multicomponent nature of PR.<sup>19</sup> Nevertheless, the COS should be updated as necessary with the rising of new evidence (eg, every 5 years).<sup>13</sup>

Future steps include defining 'how' to measure (ie, instruments to use) the proposed outcomes, as otherwise some heterogeneity might persist. This step can be addressed with a systematic review of measurement properties to identify the instruments with the best properties for each core outcome (already registered in PROSPERO, ID: CRD42022313344), and a new consensus study, if several instruments are equally robust and other aspects such as their feasibility in clinical practice, applicability across settings and charges with licensing, need to be considered.<sup>19,50</sup>

Future work could also focus on implementing strategies aiming at enhancing the COS use as uptake in most areas has been low.<sup>51</sup> Finally, clinical training on how to measure these outcomes, after the instruments are defined, might be needed as a well-qualified multidisciplinary team is desirable.

This study developed a COS for PR of people with COPD. It can now be used by different stakeholders to improve consistency and comparability of studies, benchmark PR and improve the quality of care.

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## O poder de reduzir o caos na época do RSV

Beyfortus® é o primeiro anticorpo de ação prolongada e direta desenvolvido para proteger todos os recém-nascidos e lactentes\*, contra a doença do trato respiratório inferior (DTRI) provocada pelo vírus sincicial respiratório (RSV).<sup>\*\*1</sup>

Uma **única dose** reduziu o risco de infecção do trato respiratório inferior por RSV que requer assistência médica (ITRI-RSV MA) vs. placebo em recém-nascidos e lactentes.<sup>†,‡,§,1-3</sup>

**Beyfortus®**  
(nirsevimab)

\* **Beyfortus® é indicado para a prevenção de doença das vias respiratórias inferiores causada pelo RSV em recém-nascidos e lactentes durante a sua primeira época do RSV.<sup>1</sup> Beyfortus® deve ser utilizado de acordo com as recomendações oficiais.<sup>1</sup>**

Contraindicações: hipersensibilidade à substância ativa ou a qualquer um dos excipientes.<sup>1</sup>

\*\* Beyfortus® proporciona pelo menos 5 meses de proteção contra a doença do trato respiratório inferior causada pelo RSV, com base em dados clínicos e farmacocinéticos.<sup>1</sup>

† A dose recomendada de Beyfortus® é uma dose única de 50 mg administrada por via intramuscular para lactentes com peso corporal <5 kg e uma dose única de 100 mg administrada por via intramuscular para lactentes com peso corporal ≥5 kg.<sup>1</sup>

‡ Com base nos resultados de dois ensaios multicêntricos aleatorizados, em dupla ocultação e controlados por placebo.<sup>3</sup> O **endpoint** primário foi a incidência de ITRI medicamente assistida (incluindo hospitalização), causada por RSV confirmado por RT-PCR. Eficácia demonstrada até 150 dias após a administração.<sup>1-3</sup>

– **Ensaio de fase 2b:** A população do estudo incluiu 1453 crianças grande prematuras e prematuras moderadas (IG ≥ 29 e < 35 semanas) que entravam na sua primeira época de RSV. As crianças receberam uma dose única intramuscular de 50 mg de Beyfortus® (n=969) ou placebo (n=484). Redução do risco relativo (RRR) em ITRI-RSV MA de 70,1% (IC de 95%: 52,3-81,2; p < 0,001). A incidência foi de 2,6% com Beyfortus® versus 9,5% com placebo.<sup>1,2</sup> Os tipos e as frequências dos acontecimentos adversos foram semelhantes nos grupos de Beyfortus® e de placebo.<sup>2</sup>

– **Ensaio MELODY de fase 3:** A população do estudo incluiu 3012 crianças de termo e prematuras tardias (IG ≥ 35 semanas) que entravam na sua primeira época de RSV. As crianças receberam uma dose única intramuscular de 50 mg de Beyfortus®, se peso corporal <5 kg ou 100 mg de Beyfortus® se peso corporal ≥5 kg no momento da administração de Beyfortus® (n=2009), ou de placebo (n=1003). RRR em ITRI por RSV medicamente assistida de 76,4% (IC de 95%: 62,3-85,2). A incidência foi de 1,2% com Beyfortus® versus 5,4% com placebo.<sup>1,3</sup> Os tipos e as frequências dos acontecimentos adversos foram semelhantes nos braços de Beyfortus® e placebo.<sup>3</sup>

§ As reações adversas notificadas em crianças que receberam Beyfortus® em ensaios clínicos, foram erupção cutânea, reação no local da injeção e pirexia. A ocorrência foi pouco frequente (≥ 1/1.000 a < 1/100).<sup>1</sup>

**IC**, intervalo de confiança; **IG**, idade gestacional; **DTRI**, doença do trato respiratório inferior; **ITRI**, infecção do trato respiratório inferior; **MA**, medicamente assistida; **RRR**, redução do risco relativo; **RSV**, vírus sincicial respiratório; **RT-PCR**, reação em cadeia da polimerase via transcriptase reversa.

1. Beyfortus®. Resumo das Características do Medicamento (RCM) de Beyfortus. Junho 2023

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### Informações essenciais compatíveis com o Resumo das Características do Medicamento

▼ Este medicamento está sujeito a monitorização adicional. Isto irá permitir a rápida identificação de nova informação de segurança. Pede-se aos profissionais de saúde que notifiquem quaisquer suspeitas de reações adversas através do Sítio da internet: <http://www.infarmed.pt/web/infarmed/submissao> (preferencialmente) ou através dos seguintes contactos: Direção de Gestão do Risco de Medicamentos: (Tel: +351217987373; Linha do medicamento: 800222444 (gratuita); E-mail: [farmacovigilancia@infarmed.pt](mailto:farmacovigilancia@infarmed.pt)). **Beyfortus 50 mg** solução injetável em seringa pré-cheia e **Beyfortus 100 mg** solução injetável em seringa pré-cheia. Cada seringa pré-cheia contém 50 mg de nirsevimab em 0,5 ml (100 mg/ml) e 100 mg de nirsevimab em 1 ml (100 mg/ml), respetivamente. Nirsevimab é um anticorpo monoclonal humano imunoglobulina G1 kappa (IgG1k) produzido em células de ovário de hamster Chinês (CHO) por tecnologia de ADN recombinante. **Indicações terapêuticas:** Beyfortus é indicado para a prevenção de doença das vias respiratórias inferiores causada pelo Vírus Sincicial Respiratório (VSR), em recém-nascidos e lactentes durante a sua primeira época do VSR. Beyfortus deve ser utilizado de acordo com as recomendações oficiais. **Posologia e modo de administração:** **Posologia:** A dose recomendada é uma dose única de 50 mg administrados por via intramuscular para lactentes com peso corporal <5 kg e uma dose única de 100 mg administrados por via intramuscular para lactentes com peso corporal ≥5 kg. Beyfortus deve ser administrado antes do início da época do VSR, ou desde o nascimento em lactentes nascidos durante a época do VSR. A posologia em lactentes com um peso corporal entre 1,0 kg a <1,6 kg é baseada em extrapolação, não existem dados clínicos disponíveis. Prevê-se que a exposição em lactentes com <1 kg produza exposições mais elevadas do que naqueles que pesam mais. Devem ser considerados cuidadosamente os benefícios e riscos da utilização de nirsevimab em lactentes <1 kg. Os dados disponíveis em lactentes prematuros extremos (Idade Gestacional [IG] <29 semanas) com menos de 8 semanas de idade, são limitados. Não existem dados clínicos disponíveis em lactentes com idade pós-menstrual (idade gestacional ao nascimento mais idade cronológica) com menos de 32 semanas. Em lactentes submetidos a cirurgia cardíaca com *bypass* cardiopulmonar, pode ser administrada uma dose adicional logo que se verifique estabilização do lactente após cirurgia, para garantir níveis séricos adequados de nirsevimab. Se estiverem dentro dos 90 dias, após receberem a primeira dose de Beyfortus, a dose adicional deve ser de 50 mg ou 100 mg de acordo com o peso corporal. Se decorrerem mais de 90 dias desde a primeira dose, a dose adicional pode ser uma dose única de 50 mg independentemente do peso corporal, para cobrir a época do VSR remanescente. Não existem dados de segurança e eficácia disponíveis em doses repetidas. A segurança e eficácia de nirsevimab em crianças com idade compreendida entre

os 2 e os 18 anos não foram estabelecidas. **Modo de administração:** Beyfortus é apenas para injeção intramuscular. É administrado por via intramuscular, preferencialmente na zona anterolateral da coxa. O músculo glúteo não deve ser utilizado por rotina como um local de injeção, devido ao risco de lesão no nervo ciático. **Instruções de administração:** Beyfortus está disponível em seringas pré-cheias de 50 mg e 100 mg. Consultar o RCM para instruções sobre as instruções de administração. **Contraindicações:** Hipersensibilidade à substância ativa ou a qualquer um dos excipientes. **Advertências e precauções especiais de utilização:** **Rastreabilidade:** De modo a melhorar a rastreabilidade dos medicamentos biológicos, o nome e o número de lote do medicamento administrado devem ser registados de forma clara. **Hipersensibilidade incluindo anafilaxia:** Foram observadas reações de hipersensibilidade graves, incluindo anafilaxia, com anticorpos monoclonais. Se ocorrerem sinais e sintomas de uma reação de hipersensibilidade clinicamente significativa ou anafilaxia, interrompa imediatamente a administração e inicie medicamentos adequados e/ou terapia de suporte. **Perturbações hemorrágicas clinicamente significativas:** Como com quaisquer outras injeções intramusculares, nirsevimab deve ser administrado com precaução a lactentes com trombocitopenia ou qualquer perturbação da coagulação. **Interações medicamentosas e outras formas de interação:** Os anticorpos monoclonais não têm tipicamente um potencial de interação significativo, dado que não afetam diretamente as enzimas do citocromo P450 e não são substratos de transportadores hepáticos ou renais. Não são prováveis efeitos indiretos nas enzimas do citocromo P450, dado que o alvo de nirsevimab é um vírus exógeno. **Administração concomitante com vacinas:** Considerando que nirsevimab é um anticorpo monoclonal, uma imunização passiva específica para o VSR, não se espera que interfira na resposta imunitária ativa a vacinas administradas concomitantemente. A experiência com a administração concomitante de vacinas é limitada. Nirsevimab pode ser administrado concomitantemente com as vacinas pediátricas de rotina. Nirsevimab não deve ser misturado com qualquer vacina na mesma seringa ou frasco para injetáveis. Quando administrado concomitantemente com vacinas injetáveis, devem ser administrados com seringas separadas e em locais de injeção diferentes. **Efeitos indesejáveis:** **Pouco frequentes:** Erupção cutânea; Reação no local da injeção; Pirexia. **Titular da Autorização de Introdução no Mercado:** AstraZeneca AB, SE-151 85 Södertälje, Suécia. **Representante local do Titular da Autorização de Introdução no Mercado:** Sanofi – Produtos Farmacêuticos, Lda, Empreendimento Lagoas Park Edifício 7 - 3º Piso, 2740-244 Porto Salvo, Portugal. Informações revistas em março 2023. **Para mais informações deverá contactar o representante local do titular da Autorização de Introdução no Mercado. Medicamento sujeito a receita médica.** Versão 2.0 (março 2023).

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