

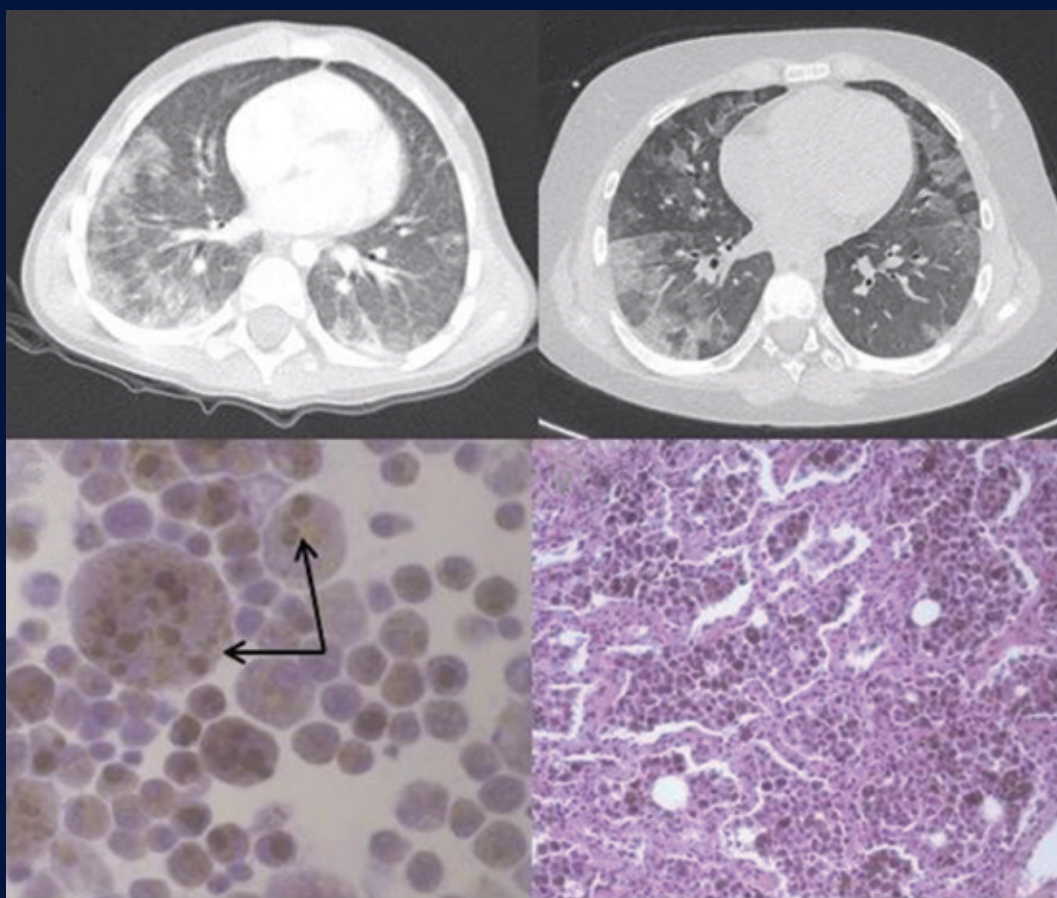
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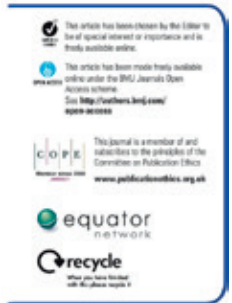
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Editorial

Doenças não transmissíveis, fatores de risco e desencadeantes de agudizações ou, também, favorecedores de expressão de doença crónica. E a infeção a ocupar um lugar central no desencadear de exacerbações, de consumo de recursos de saúde e na orientação de terapêuticas.

Na página 12, a Asma e a falta de associação com fatores socio-económicos num País do Norte da Europa. Seriam estes resultados reprodutíveis em outros?

Na página 7, as intervenções terapêuticas e custos associados ao consumo de recursos hospitalares. Uma tendência que irá modelar as intervenções médicas do futuro de forma explícita?

O capítulo das infeções respiratórias exprime um potencial presente e futuro de reconhecimento de cargas virais, expressões moleculares. Será que este conhecimento se irá refletir, num futuro próximo, no aparecimento de terapêuticas farmacológicas e intervenções de outra natureza para a profilaxia e tratamento das infeções respiratórias, que são das maiores responsáveis por doença aguda na atualidade? Talvez o futuro seja agora...

Na página 34, de novo a nossa colega, Dr Sanja Stanojevic, a refletir sobre resultados de espirometria como *outcomes* de monitorização e intervenção e assim não é indiferente, na criança, a determinação da variabilidade longitudinal dos resultados para apreciação de agravamento ou melhoria. A refletir na prática clínica.

E finalmente a diáda, jovens e tabaco, aqui com um estudo que chama a atenção para a existência de anúncios subtis na outra indústria, a cinematográfica, que como sabemos tem uma influência na modelação dos gostos e costumes. A ler no artigo da página 39.

Para terminar, na página 46, a discussão sobre a duração de terapêutica antibiótica na bronquite bacteriana prolongada. Esta situação clínica, com descrição recente, terá porventura implicações a longo prazo, nomeadamente na prevalência de bronquiectasias. Seis semanas de antibiótico e não 2.... Seguramente um desafio para a adesão à terapêutica

São inúmeras as razões para ler atentamente e com detalhe esta publicação.
Desejamos boas leituras, e que possamos reencontra-nos em breve.

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A oxigenoterapia de alto fluxo de primeira linha na bronquiolite não implica uma redução de custos para o serviço de saúde

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RESUMO

Contexto A bronquiolite constitui a principal causa de internamento hospitalar infantil. A oxigenoterapia de alto fluxo tem surgido como um novo tratamento. No entanto, a relação custo-eficácia da sua utilização como terapêutica de primeira linha é desconhecida.

Objetivo Comparar o custo de fornecimento de terapia de alto fluxo enquanto terapia de primeira linha e a terapêutica de resgate após insuficiência de oxigênio padrão no tratamento da bronquiolite.

Métodos Uma avaliação econômica de um ensaio do ponto de vista dos serviços de saúde, utilizando dados de um ensaio aleatorizado, controlado e multicêntrico para crianças com hipoxemia (≤ 12 meses) admitidas em hospital com bronquiolite na Austrália e na Nova Zelândia. Os custos de intervenção, a duração da hospitalização e cuidados intensivos e os custos associados foram comparados em crianças que receberam tratamento de primeira linha com terapêutica de alto fluxo (alto fluxo precoce, $n=739$) ou em crianças que receberam oxigênio padrão e resgate opcional de alto fluxo (resgate de alto fluxo, $n=733$). Os custos foram aplicados com base em fontes de custos australianas, sendo reportados em dólares australianos de 2016–2017 (AU\$).

Resultados O custo incremental para evitar uma insuficiência de tratamento foi de AU\$1778 (95% de intervalo credível (Icr) 207 a 7096). O custo médio do tratamento da bronquiolite, incluindo custos de intervenção e custos associados à duração da estadia, foi de mais AU\$420 (95% Icr - 176 a 1002) por criança no grupo de alto fluxo inicial em comparação com o grupo de alto fluxo de resgate. Verificou-se uma probabilidade de 8% (95% Icr - 7,5 a 8,6) de a terapêutica precoce de alto fluxo de oxigênio ser mais vantajosa em termos econômicos.

Conclusões É pouco provável que a utilização de oxigênio de alto fluxo como terapêutica inicial para insuficiência respiratória em crianças com bronquiolite seja economicamente vantajosa para o sistema de saúde, em comparação com a oxigenoterapia de padrão.

INTRODUCTION

Bronchiolitis is one of the most common illnesses affecting infants, with 2%–3% of all children requiring hospital admissions during their first year of life, and globally represents a major cause of infant morbidity and mortality.^{1–3} In high-income countries, approximately one in eight infants hospitalised with bronchiolitis requires admission to an intensive care unit (ICU).⁴ In the USA, bronchiolitis accounts for 21% of hospital admissions for infants, with an estimated annual hospitalisation cost of US\$1.7 billion.^{5,6} In Australia and New Zealand, there has been an increase in ICU admissions. Between 2002 and 2014, 28% of non-elective paediatric ICU admissions were due to bronchiolitis, and the annual cost of bronchiolitis admission requiring intensive care increased by US\$30 million over the past decade.⁴

What is already known on this topic?

- The use of high-flow oxygen therapy has increased in infants with bronchiolitis to provide humidified oxygen.
- Little is known about the costs and cost-effectiveness of high-flow as initial therapy compared with standard oxygen therapy in infants with bronchiolitis.

What this study adds?

- The analysis used data from the PARIS trial in bronchiolitis and provides a comprehensive analysis of costs related to bronchiolitis management in infants.
- High-flow oxygen therapy as initial therapy for respiratory failure in infants with bronchiolitis is unlikely to be cost saving to the health system compared with standard oxygen with the option of rescue high-flow.

Hospital management of infants with bronchiolitis focuses on maintenance of hydration and respiratory support² with a trend towards reduced intubation and ventilation, and increased use of non-invasive ventilation.⁷ High-flow is a rapidly emerging therapy providing non-invasive respiratory support both within and outside ICU. It delivers heated and humidified air blended with oxygen via the nasal passages, providing positive pressure, reducing the infant's work of breathing and providing dead space washout of CO₂ in the upper airway.⁵

Over the last decade, high-flow has gained popularity in clinical practice, particularly in Europe, North America and Australasia.^{8,9} Observational and randomised trials of high-flow compared with standard oxygen therapy indicated a good safety profile.^{10,11} While initial non-experimental studies suggested a reduction in ICU admission rates,¹⁰ this finding was not replicated in two recent randomised controlled trials (RCTs) which reported no difference in ICU admission or hospital length of stay.^{11,12}

In the absence of evidence suggesting superior long-term clinical or patient-relevant outcomes associated with high-flow in bronchiolitis, its implementation in clinical practice should be guided by its comparative efficiency in managing an acute bronchiolitis episode. Little is known about the costs and cost-effectiveness of high-

Table 1 Unit costs used to value resource use measured in the main trial analysis

Resource item	Unit	Unit cost (AUS)	Source
High-flow capital equipment (AIRVO2 system)	Item	2795.00	Manufacturer
Consumables for high-flow therapy			
Paediatric circuit	Item	55.50	Manufacturer
Paediatric nasal cannula (Optiflow)	Item	25.00	Manufacturer
Oxygen tubing	Item	7.50	Manufacturer
Wiggle pads	Item	3.00	Manufacturer
Consumables for standard oxygen therapy			
Paediatric nasal cannula	Item	2.64	Manufacturer
Bronchiolitis treatment			
Bronchiolitis treatment and LoS	Episode of care (AR-DRG code E70A)*	Varies	National Efficient Price Determination ¹⁵
Retrieval and transfer costs			
Road transfer in Queensland (fixed)	Retrieval	832	Queensland Health Ambulance
Nurse time (grade 6.4)	Hour	61.64	Queensland Health ¹⁸
Medical practitioner time (L8)	Hour	80.94	Queensland Health ¹⁹

*AR-DRG is Australian Refined Diagnosis Related Group; Code E70A is Bronchiolitis with Complications. Price determination varies dependent on the length of stay (disaggregated by hospital and intensive care unit), indigenous status and remoteness of the patient. LoS, length of stay.

-flow compared with standard oxygen in infants with bronchiolitis.

We recently published the findings of the Paediatric Acute Respiratory Intervention (PARIS) trial, which compared initial high-flow oxygen therapy to initial standard oxygen with the option to use rescue high-flow in infants with bronchiolitis.^{11 13} The present paper reports a pre-planned economic evaluation based on data collected alongside the PARIS trial, which aims to compare the cost of providing of these therapies for infants with bronchiolitis.

METHODS

Participants and trial design

PARIS was an open-label, non-blinded multicentre RCT in hypoxemic infants with bronchiolitis, less than 12 months of age, admitted to hospital.^{11 13} In total, 1472 infants were randomly allocated (1:1 ratio) a treatment; either high-flow as initial therapy (early high-flow group) or standard oxygen with

the option to escalate to high-flow (rescue high-flow group). In the early high-flow group, infants received heated and humidified nasal high-flow delivered by the Optiflow system (Fisher and Paykel Healthcare, New Zealand; n=739) at a rate of 2L/kg/min. Infants started on standard oxygen received oxygen via nasal cannula up to 2L/min (n=733). Escalation to rescue high-flow was permitted when infants failed standard oxygen. The study took place in emergency departments and general paediatric wards in 17 hospitals in Australia and New Zealand between October 2013 and August 2016. Ethics approval was granted by the Children Health Services Queensland Human Research Ethics Committee (HREC/13/QRCH/93). The trial was registered prospectively on the Australian New Zealand Clinical Trials Registry (ACTRN12613000388718).

The primary outcome of the clinical trial was the proportion of infants in each group with treatment failure. Treatment failure of either standard oxygen or high-flow therapy arm is defined as meeting three out of four specified failure criteria requiring escalation of treatment or high level of care such as high acuity or intensive care.¹³ Secondary outcomes included the intubation rates and length of hospital stay. The trial reported an 11% decrease (95% CI -15% to -7%) in the escalation of care due to treatment failure when high-flow was used early during admission compared with standard oxygen, but no significant difference was observed in some of the secondary outcomes.¹¹

Estimating resource use and costs

The resources costed included resources used to deliver high-flow, the treatment of bronchiolitis for the hospital length of stay (disaggregated by ICU and ward stay) and retrieval and transport events observed in the trial. Costs were measured from the healthcare service perspective in 2016–2017 Australian Dollars (AU\$). Given the short time horizon, costs were not discounted.

Intervention costs

The intervention resources included capital equipment and consumables (online supplementary table 1). Quantities of consumables used were multiplied by unit costs (table 1), summed to generate a total consumables cost and divided by the number of infants who received high-flow to generate a weighted cost per infant. The capital equipment cost per infant was estimated based on an assumed 5-year equipment lifespan with a machine utilisation rate of 80%. An 80% utilisation rate was assumed based on the rate adopted in a previous economic study.¹⁴ We performed sensitivity analyses around this assumption by varying utilisation rate and equipment lifespan. Infants in standard oxygen were costed for one paediatric nasal cannula.

We assumed no difference in the time taken to establish an infant onto either early high-flow or standard oxygen, and the ward:nursing ratio for both arms remained the same throughout the trial (1:4). Nasogastric tube (NGT) usage and enteral nutrition was not captured, and it was anticipated that there was minimal cost difference between the two groups due to NGTs being a low-cost item.

Bronchiolitis treatment costs

Infants who remained on high-flow or standard oxygen in the ward were costed for their length of stay (until the point of hospital discharge) based on assumed Australian Refined Diagnosis Related Group (AR-DRG) prices for Bronchiolitis with Complications (E70A; table 1).¹⁵ Patient postcodes were used to adjust for remoteness area boundaries.¹⁶

Infants who received standard oxygen and escalated to highflow but remained in the ward were costed for high-flow in addition to the cost per general bed-day. Infants who were escalated to ICU were costed for the amount of time in ICU.

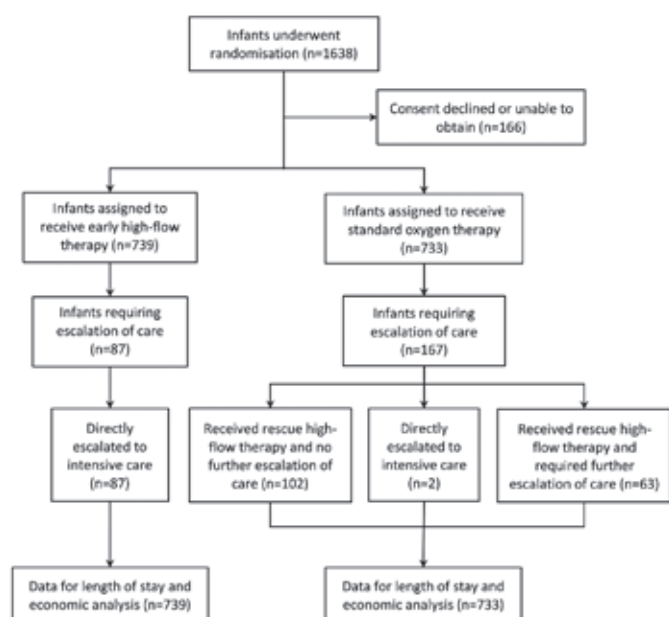


Figure 1 Flow diagram of the randomisation trial from enrolment until hospital discharge.

Table 2 Key resource (hospital length of stay) measured in the trial¹¹

Item of resource use	Early high-flow group	Standard oxygen±rescue high-flow group	Mean difference (95%CI)*x
Total HLoS in days	(n=739)	(n=733)	
Mean (SD)	3.12 (2.43)	2.94 (2.73)	0.18 (−0.09 to 0.44)
Median (IQR)	2.50 (1.71–3.90)	2.20 (1.48–3.55)	-
HLoS for those who failed treatment and received escalation of care (days)	(n=87)	(n=167)	
Mean (SD)	5.82 (2.77)	4.95 (4.13)	0.87 (−0.09 to 1.85)
Median (IQR)	5.37 (3.71–7.31)	4.0 (2.69–5.81)	-
HLoS for those who did not require escalation of care (days)	(n=652)	(n=566)	
Mean (SD)	2.76 (2.14)	2.35 (1.75)	0.41 (0.18 to 0.63; p<0.001)
Median (IQR)	2.23 (1.60–3.37)	1.88 (1.36–2.81)	-
HLoS for those who failed treatment and transferred to ICU (days)	(n=87)	(n=65)	
Mean (SD)	5.82 (2.77)	6.19 (5.30)	−0.36 (−1.67 to 0.95)
Median (IQR)	5.37 (3.71–7.31)	4.66 (3.06–6.88)	-
ICU length of stay (days)	(n=87)	(n=65)	
Mean (SD)	2.63 (1.70)	2.72 (2.31)	−0.09 (−0.74 to 0.55)
Median (IQR)	2.22 (1.50–3.54)	2.02 (1.34–2.98)	-
Duration of high-flow therapy (days)†	(n=728)	(n=162)	
Mean (SD)	1.85 (1.70)	2.26 (2.09)	0.41 (−0.71 to −0.11; p=0.008)
Median (IQR)	1.38 (0.74–2.40)	1.62 (1.04–2.70)	

*Student's t-test of independent samples was used.

†Data on the duration of high-flow therapy were missing for 3 patients in the standard oxygen group and 11 in the high-flow group.

HLoS, total hospital length of stay—ie, in general ward and intensive care unit (ICU); IQR, interquartile range; SD, standard deviation.

Retrieval and transport costs

Interhospital transport for infants with bronchiolitis is commonly used in the sites participating in the study.¹⁷ Transport costs were included for infants requiring transfer to a higher level of care. All transfers were by road. Considering most retrievals occurred in South East Queensland, Queensland Health wage rates were used to cost the time taken to retrieve each infant.^{18 19}

Within-trial economic analysis

We undertook a cost-minimisation analysis from the healthcare provider perspective using data from the PARIS trial to compare the cost of providing initial high-flow to that of standard oxygen including the option for rescue high-flow, as detailed in the trial protocol.¹³ The analysis estimated the costs for the bronchiolitis episode of care until the point of discharge home. This assumes an equivalent clinical outcome at the point of discharge. To establish within-trial cost-effectiveness, we assessed the direct hospitalisation-related costs in infants with bronchiolitis and calculated the incremental cost based on the primary outcome, that is, to avoid a treatment failure.

We used guidelines for performing economic evaluation alongside clinical trials.²⁰ For the base case analysis, Australian unit costs were applied to all resources used regardless of the trial site. Subgroup analyses were conducted to examine the differential mean cost for pre-specified infant subgroups; born prematurely (<37 weeks' gestation), previous hospital admission for respiratory disease, congenital heart defect, age group (≤3, 3–6, >6 months) and infants presenting to hospitals with/without an on-site ICU.¹³

We used non-parametric bootstrapping (10000 replications) to estimate uncertainty using 95% credible intervals (CrIs) around the point estimates and the probability that early highflow was cost saving compared with standard oxygen with rescue high-flow.

Sensitivity analyses

We performed sensitivity analyses for the different healthcare systems, in which we computed costs for the two New Zealand (NZ) study sites using price weights based on NZ's case-mix framework for publicly funded hospitals for 2016–2017 (online supplementary table 2).²¹ Costs (NZ\$) were then converted to

Australian dollars (AU\$0.95=NZ\$1 based on average exchange rates in 2016–2017).²² There were no hospital transfers in the NZ. We explored the impact of assumptions made related to high-flow equipment by varying the equipment utilisation rates between 10% to 100% (base case 80%) and the lifespan between 2 and 10 years (base case 5 years).

RESULTS

Resource use

Of the 1472 infants enrolled, 739 were randomised to early high-flow with 87 of these receiving escalation of care (all to ICU; figure 1). A further 733 infants were randomised to initially receive standard oxygen, with 167 of these receiving escalation of care, 165 of whom received rescue high-flow as part of the escalation. Baseline demographic and physiological characteristics of the infants were similar between study groups.¹¹ There was no significant difference in total hospital stay between groups across the whole trial cohort or in infants who failed their initial treatment and received escalated care (table 2).¹¹ However, in infants who did not require escalation of care, those receiving early high-flow had a longer hospital stay (0.41 days) than those on standard oxygen (p<0.001). No significant difference in length of stay in ICU between groups was shown for infants admitted to ICU as part of the escalation of care (table 2). Standard oxygen group who received rescue high-flow were treated with high-flow for a mean of 0.41 (95% CI 0.11 to 0.71, p=0.008) days longer than those who received early high-flow.

Within-trial economic analyses

Initial intervention costs were higher for the early high-flow (AU\$139.21 per infant) than for initial standard oxygen prior to escalation (AU\$2.64 per infant; table 3). The mean cost of oxygen therapy overall was higher per infant for early highflow (AU\$139.21±11.73) compared with standard oxygen with the option of rescue high-flow (AU\$33.79±58.54; p<0.001). Thirty-five infants required a transfer from regional hospitals to tertiary centres. Mean retrieval time was 5.46±1.55hours in early high-flow (20 infants) and 5.21±1.0hours in standard oxygen with rescue high-flow group (15 infants, p=0.59).

The incremental cost to avoid one treatment failure amounted to AU\$1778 (95% CrI 207 to 7096). This relates to total per person cost of each intervention arm from enrolment to discharge for res-

Table 3 Comparison of costs and effects per infant between highflow and standard oxygen therapy (AU\$)

	Early high-flow group (n=739)	Standard oxygen±rescue high-flow group (n=733)
A. Initial intervention cost per infant		
Capital cost of high-flow equipment, mean (SD)	3.53 (3.23)	-
Consumables, mean (SD)	136.61 (0.00)	2.64
(A) Total intervention cost per infant (capital+consumables), mean (SD)	139.21 (11.73)	2.64
B. Costs for rescue high-flow therapy (n=165)		
Capital (high-flow equipment) for those receiving rescue high-flow, mean (SD)	-	4.32 (3.97)
Consumables for those receiving rescue highflow, mean (SD)	-	136.61 (0.00)
(B) Total costs associated with rescue high-flow therapy, mean (SD)	-	141.01 (19.30)
C. Costs associated with length of stay for bronchiolitis episodes of care, mean (SD)		
Cost of hospital length of stay-non-ICU stay, mean (SD)	5552 (1593)	5596 (1970)
Cost of ICU stay for those with an ICU stay, mean (SD, n)	13 415 (8679, n=87)	13 889 (11 823, n=65)
(C) Total costs associated with bronchiolitis episode of care, mean (SD)	7131 (5469)	6827 (5701)
D. Hospital transfer and retrieval cost, mean (SD, n)		
	2442 (221, n=20)	2406 (142, n=15)
E. Total cost per infant (A+B+C+D)		
Mean (SD)	7314 (5586)	6893 (5809)
Median (IQR)	5568 (5567–5572)	5431 (5431–5569)
Differential mean cost (95% CrI)*	420 (–176 to 1002)	
F. Total cost up to treatment failure or until discharge if responder		
Mean (SD)	5681 (1575)	5492 (584)
Median (IQR)	5568 (5567–5572)	5431 (5431–5569)
Differential mean cost (95% CrI)*	189 (67 to 311)	
G. Effectiveness		
Treatment failure rate	0.118 (0.094 to 0.141)	0.228 (0.197 to 0.258)
Differential treatment effect (95% CrI)*	-0.118 (-0.072 to -0.148)	
H. Cost-effectiveness ratio, ie, mean incremental cost per treatment failure avoided, F/G (95% CrI)		
	1778 (207 to 7096)	

The incremental cost per treatment failure avoided in the table is close to but not exactly equal to the difference in cost divided by the difference in effectiveness, due to the bootstrapping method employed and rounding error.

*95% non-parametric credible interval based on 10 000 bootstrap replications.
ICU, intensive care unit; IQR, interquartile range; SD, standard deviation.

ponders and from enrolment to escalation of care for nonresponders. Overall, the early high-flow group cost a mean of AU\$420 (95% CrI –176 to 1002) more per infant. There was an 8% (95% CrI 7.5% to 8.6%) likelihood of early high-flow being less costly than standard oxygen with rescue high-flow. The absolute mean cost differed across subgroups defined by infant age, prematurity, history of a congenital heart defect and level of the hospital but not by the previous admission for respiratory disease (table 4). No significant differences in mean cost per infant between study groups within any one subgroup were evident.

Sensitivity analysis

The mean costs for both early high-flow and standard oxygen with rescue high-flow were slightly lower when NZ sites were costed using NZ prices (online supplementary table 3). The mean differential costs were similar (AU\$435; 95% CrI –110 to 967). As the capital costs associated with the high-flow machine were low (AU\$3.53 per infant assuming an 80% utilisation rate) compared with overall costs, changes in high-flow machine utilisation rates had minimal impact on the differential cost between the groups (online supplementary table 4).

DISCUSSION

This economic analysis used data from the PARIS trial and found higher costs per infant treated with high-flow compared

Table 4 Variation in mean total costs (AU\$) per infant treated by subgroups

Subgroup	Early high-flow group	Standard oxygen±rescue high-flow group	Mean cost difference (95% CrI)*
Prematurity <37 weeks			
Yes	8233 (n=137)	7519 (n=128)	714 (–1025 to 2278)
No	7104 (n=602)	6761 (n=605)	343 (–267 to 951)
Age group			
≤3 months	8285 (n=211)	8196 (n=186)	89 (–1438 to 1570)
>3 to 6 months	7172 (n=187)	6395 (n=170)	777 (–75 to 1669)
>6 months	6790 (n=341)	6475 (n=377)	315 (–415 to 1008)
Hospital levels			
On-site ICU	7578 (n=469)	7089 (n=486)	489 (–271 to 1208)
No on-site ICU	6854 (n=270)	6508 (n=247)	345 (–638 to 1253)
Previous hospital admission for respiratory disease			
Yes	7558 (n=187)	6792 (n=225)	766 (–467 to 1953)
No	7231 (n=552)	6938 (n=508)	293 (–394 to 949)
Congenital heart defect			
Yes	9538 (n=8)	10 394 (n=16)	–855 (–9816 to 8066)
No	7289 (n=731)	6815 (n=717)	474 (–86 to 1040)

*95% non-parametric credible interval based on 10 000 bootstrap replications.
ICU, intensive care unit.

with the standard oxygen with rescue high-flow; this difference did not reach statistical significance at conventional 5% levels. Nevertheless, early high-flow provided as first-line therapy for hypoxic infants with bronchiolitis had a very low likelihood (8%) of being a lower-cost therapy. The subgroup analyses showed that costs for the management of bronchiolitis in infants differ slightly across patients, but early high-flow was not proven to be cost saving for any subgroup. Moreover, relaxing assumptions made around the use of country-specific costs or the utilisation rate of the high-flow equipment did not substantially impact findings.

The costs associated with length of hospital stay dominated the overall cost per infant. Previous cost estimates in larger bronchiolitis cohorts were based on summary data from large health-care databases.⁴⁶ We used individual patient-level data to estimate the cost of bronchiolitis. Since total hospital length of stay was similar between the groups in the PARIS trial, it is not surprising that this evaluation was unable to show that the additional intervention costs of high-flow, though small, would be offset by any savings associated with the reduced escalation rate that was reported by the PARIS trial in the early high-flow group (compared with standard oxygen). Likewise, the mean length of ICU stay for those who failed initial treatment (high-flow or standard oxygen) was similar between the groups. There may be benefits for patients and their families associated with high-flow that has not been considered in this analysis. The patient and family experience with high-flow is an important area for future research.

A recent trial¹² found that high-flow was cost saving compared with standard oxygen in bronchiolitis. However, the study recruited infants aged up to 24 months in contrast to 12 months in this study, and the analysis assumed similar hospitalisation costs (emergency department, ward and ICU) per patient. Our analysis included a much larger sample of sicker patients from 17 sites in two countries, and we include other costs such as retrievals. In a further study, Heikkilä²³ used data from a retrospective case-control study to estimate the cost-effectiveness of high-flow in infants with bronchiolitis, compared with standard oxygen. Using a decision model, the authors found that high-flow was cost saving. This was contributed by lower ICU admission rates and consequential costs in the high-flow group. However, these lower rates of ICU admission have not been found in the two RCTs conducted to date.^{10 11}

Strengths and limitations

Our study investigated costs to the point of hospital discharge and assumed no difference in long-term outcomes irrespective of

the treatment received. As bronchiolitis is a self-limiting illness without long-term sequelae, we consider this approach reasonable. Our analysis did not consider family or community costs associated with the illness. Retrieval costs were comparatively low as transfer did not require any rotary or fixed-wing retrievals. Likewise, the analysis assumed similar medical and nursing care per patient ratios.

The primary outcome of the clinical trial was defined as an escalation of therapy, whereas the cost-minimisation analysis encompassed the entire stay in the hospital, including the crossover from standard oxygen to high-flow. The clinical trial¹¹ reported high-flow to be associated with a lower escalation rate compared with initial standard oxygen. We did not collect data on patient-reported outcomes, and we cannot comment on whether the quality of life or satisfaction may be perceived to be better with high-flow or standard oxygen. Long-term outcome data in infants with bronchiolitis is only available in patients who received mechanical ventilation and impaired neurodevelopment in these infants was related to the sedation used during paediatric ICU.²⁴

The PARIS trial on which this analysis is based was large, recruiting over 1400 infants; and yet the findings related to costs are inconclusive. A study with a sufficient sample size to be powered to show a difference in costs at conventional significance levels is likely to be prohibitively expensive to run. It shows that the costs associated with high-flow constitute a small proportion of the overall costs of hospitalisation for bronchiolitis.

Implications for practice

It is unlikely that early high-flow represents value for money compared with standard oxygen with rescue high-flow when it is used as a first-line treatment for infants admitted to hospital with bronchiolitis. Higher costs for the high-flow stem to a lesser extent from equipment costs, but more from a longer length of stay in the hospital, particularly for those who did not require escalation of care.

CONCLUSIONS

Routine implementation of early high-flow as first-line therapy for the management of bronchiolitis in infants under 12 months cannot be recommended from a healthcare cost perspective. Future studies should investigate if provision of high-flow to selected patient groups at higher risk of requiring intensive care would be cost-effective as second-line therapy.

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ARTIGO ORIGINAL INVESTIGAÇÃO

Asma e mortalidade por todas as causas em crianças e jovens adultos: um estudo de base populacional

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RESUMO

Contexto Estudos sugerem um aumento da mortalidade por todas as causas entre adultos com asma. O nosso objetivo foi estudar a relação entre a asma em crianças e adultos jovens e a mortalidade por todas as causas e investigar as diferenças na taxa de mortalidade pelo facto de também apresentar uma doença limitadora de vida (LLC, do inglês *life-limiting condition*) ou por estatuto socioeconómico (ESE) parental.

Métodos No presente estudo baseado em registos estão incluídos 2 775 430 indivíduos nascidos na Suécia entre janeiro de 1986 e dezembro de 2012. Identificámos casos de asma utilizando o *National Patient Register* (NPR) e o *Prescribed Drug Register*. Os indivíduos com LLC foram identificados utilizando o NPR. Os ESE parentais à nascença (rendimentos e educação) foram retirados de *Statistics Sweden*. Estimámos a associação entre asma e mortalidade por todas as causas utilizando um modelo de riscos proporcionais de Cox. A modificação do efeito por LLC ou ESE parental foi estudada utilizando termos de interação no modelo ajustado.

Resultados A taxa de risco ajustada (adjHR) para mortalidade por todas as causas em casos de asma *versus* casos de não asma foi de 1,46 (95% IC 1,33 a 1,62). A taxa mais elevada parecia ser para os sujeitos entre 5 e 15 anos de idade. Nas pessoas com asma e sem LLC, a adjHR manteve-se elevada com 1,33 (95% IC 1,18 a 1,50), mas diferiu ($p=0,002$) das pessoas com asma e LLC, com uma adjHR de 1,87 (95% IC 1,57 a 2,22). Os ESE parentais não alteraram a associação (rendimento, $p=0,55$; educação, $p=0,83$).

Conclusão Este estudo demonstra que a asma está associada a um aumento da mortalidade em crianças e jovens adultos, independentemente de LLC ou do ESE parental. É necessária mais investigação para analisar os possíveis mecanismos para esta associação.

INTRODUCTION

All-cause mortality and asthma-specific mortality in children and young adults have reduced in the past decades in Europe and other high-income countries globally.^{1,2} In Sweden, both child mortality and asthma-specific mortality are low.^{3,4} As in other Northern European countries, the leading causes of death in Sweden in childhood and adolescence are road injuries, congenital birth defects and neoplasms.^{1,5} Morbidity among children and young adults in Western Europe is increasingly dominated by non-communicable disease, where asthma is a significant contributor.⁵

The worldwide reduction in asthma-specific mortality is attributed to widespread use of inhaled corticosteroids (ICS) after its introduction in the 1980s.^{2,6} Only 37 deaths from asthma in Sweden were reported for persons aged 1–34 years from 1994 to 2003.⁴ A study on asthma-specific mortality using data from WHO

Key messages

What is the key question?

► Is asthma associated with increased all-cause mortality rate in children and young adults and does it differ for those with or without life-limiting conditions or by parental socioeconomic status at birth?

What is the bottom line?

► The results suggest that asthma increases all-cause mortality also in children and young adults, and while having a life-limiting condition appears to be an important effect modifier for the association between asthma and all-cause mortality, parental socioeconomic status did not alter the association.

Why read on?

► To our knowledge, this is the largest population study of children and young adults on this topic, and this study contributes to the further understanding of the association between asthma and all-cause mortality.

Mortality Database showed that age-standardised mortality in Sweden for persons aged 5–34 years in Sweden has continued to fall.⁶

Although asthma-specific mortality has reduced, there are studies which suggest that having asthma increases the risk of all-cause mortality in adults.^{7,8} A cohort study in Finland found that persons over 30 years of age with asthma were at higher risk of all-cause mortality.⁷ Furthermore it has been shown that adults with asthma are more likely to die from chronic conditions than individuals without asthma.⁸ Results from a recent cohort study from Scotland demonstrate there is also an increased all-cause mortality among children with asthma.⁹ However, the relationship between asthma and all-cause mortality in children and young adults is not as extensively studied and is clearly not fully understood.

Asthma is a chronic condition characterised by symptoms such as wheezing and coughing.¹⁰ The prevalence among Swedish children is around 10%.¹¹ Asthma is known to be comorbid with diseases such as allergic rhinitis, attention deficit hyperactivity disorder and obesity,^{10 12–14} and it has also been shown that persons with asthma more commonly have other chronic conditions than those without asthma.¹⁵ Chronic conditions also comprise life-limiting conditions, defined as conditions ‘without a reasonable hope of cure’.¹⁶ Studies from the UK show a rising prevalence of children and

young adults with a life-limiting condition, and chronic conditions are increasingly found among children who die.^{16 17}

It is well established that disadvantaged socioeconomic status (SES) is associated with an increase in childhood mortality.¹⁸ Income, education and occupation are often used as measures of SES.¹⁹ Low SES and factors related to low SES have been shown to increase all-cause mortality in young children, older age groups and asthma-specific mortality.^{3 7} In Sweden, deaths due to asthma have been linked with poor compliance with asthma treatment and substance misuse, both of which are associated with disadvantaged SES.⁴ Low parental SES has also been implicated in the development of asthma in childhood, an increased prevalence of severe asthma and a decreased amount of dispensed controller medication.^{19–21}

It is of interest to healthcare providers and policy makers to understand the relationship between asthma, all-cause mortality, life-limiting conditions and parental SES. Hence, the aim of this study was to investigate the association between asthma and all-cause mortality in children and young adults aged 1–25 years and explore if this effect was different for those with or without life-limiting conditions or by parental SES at birth. The hypothesis was that asthma increases all-cause mortality in children and young adults and that a life-limiting condition and parental SES alter this effect.

METHODS

Study design and population

This was a register-based cohort study of individuals born in Sweden. Information was gathered from four registers held by the Swedish National Board of Health and Welfare: the Medical Birth Register (MBR), the National Patient Register (NPR), the Prescribed Drug Register (PDR) and the Swedish Cause of Death Register. Information from four registers held by Statistics Sweden was also used. These were the Multi-Generation Register (MGR), the Total Population Register (TPR), the Income and Taxation register (IOT), and the Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA by Swedish acronym). All data from the study individuals and their parents were linked using the personal identification number, a unique identifier held by every person residing in Sweden (online supplemental figure S1).

The study population consists of all individuals born in Sweden between 1 January 1986 and 30 December 2012 (n=2 795 154) identified from the MBR (which reports 99% of all births since 1973).²² Those who died (n=10 757, 0.4%) or emigrated (n=8967, 0.3%) during their first year of life were excluded, resulting in a cohort of 2 775 430 study individuals. Mothers and fathers were linked to the study individuals through the MGR.

Exposure

Asthma cases were identified using data from two registers, the NPR and the PDR, and we based on doctors' diagnosed asthma and/or on dispensed asthma medications from a doctor's prescription according to a previously published validation study.¹¹ Asthma was defined up to 1 July 2005 using the NPR only, which covers all inpatient hospital care from 1987 and 75% of outpatient visits from 2001. From 1 July 2005 asthma was defined by an algorithm used in a previous validation study, using the NPR as well as the PDR, which covers all prescribed drugs dispensed at pharmacies in Sweden.^{11 22} From the NPR, asthma cases and incidence dates were defined as the first hospital admission or outpatient visit, with a primary or secondary diagnosis of asthma identified using the corresponding code from the International Classification of Diseases (ICD). For ICD-9 code 493 was used and for ICD-10 codes J45 and J46 were used. From the PDR, an asthma case was identified by the dispensed asthma medications, ICS, β -agonists, combination products or leukotriene receptor antagonists, using the following corresponding ATC codes (Anatomic Therapeutic Chemical classification codes): R03BA, R03AC, R03AK and R03DC, respecti-

vely. A record of at least two dispensed prescriptions of asthma medications was required to be identified as an asthma case using the PDR. Although it could lead to underestimation of the association, in order to avoid immortal time bias the incident date was determined by the date of the second dispensed prescription. In instances where an individual had an incident date recorded in both the NPR and the PDR, the earliest date was used.

Outcome

The cohort was linked to the Swedish Cause of Death Register, a register with a high level of completeness and where all deaths from 1961 are recorded.²³ Data collected included the date of death and cause of death. The outcome, all-cause mortality, was defined as any cause of death which occurred between the study individual's 1st and 25th birthday. The cause of death was identified by the corresponding ICD code and was used for descriptive purposes only.

Covariates

The covariates were chosen using a directed acyclic graph (online supplemental figure S2).²⁴ From the MBR we obtained data relating to the study individuals' characteristics: sex, prematurity, if they were born small for gestational age (SGA) and calendar year of birth. From the NPR we identified those with a life-limiting condition, using the ICD-10 code and the corresponding ICD-9 code, based on the definition used by Fraser *et al*¹⁶ (online supplemental table S1), which includes neurological conditions, congenital and chromosomal abnormalities. The earliest date of diagnosis was used in instances where an individual had more than one life-limiting condition.

Covariates relating to family characteristics, maternal age at delivery, smoking during first pregnancy trimester and maternal country of birth were retrieved from the MBR and the TPR.

Data on parental SES (income and education) were obtained using the IOT register and the LISA database. Both LISA and IOT are updated annually and these registers record data on individuals 16 years or older living in Sweden. The IOT register contains information regarding income only; it was established in 1968. In 1990 LISA was established and IOT was integrated into this database, which also contains information on education.²⁵

Parental income was defined as the highest parental disposable income in the year before the birth of the study individual, divided into quintiles. Parental education was defined as the highest attained education between each parent in the year of the birth of the study individual. Parental education data for study individuals born before the LISA database started (1986–1989) were defined according to data from LISA in 1990. Parental education was categorised as compulsory school (≤ 9 years), high school (10–12 years) or college/further education (> 12 years).

Statistical analysis

The study individuals were followed from their first birthday until end of follow-up, which was defined as their 25th birthday, date of death, emigration date or 31 December 2013, whichever occurred first. Crude mortality rates per 100 000 person years with 95% CI by asthma exposure were first calculated, assuming a Poisson distribution.

The Cox proportional hazards model was then used to estimate HR with 95%CI, comparing all-cause mortality in those with and without asthma. Asthma was treated as time-varying exposure in all analyses, whereby an individual contributed towards 'no asthma' time-at-risk before being identified as an asthma case and towards 'asthma' time-at-risk if and from the time they were identified as an asthma case. Attained age was the underlying timescale used for survival analyses.

Both an unadjusted model and a model adjusted for covariates were fitted. These covariates were sex, prematurity, SGA, life-limiting condition, calendar year of birth, maternal age at delivery, maternal smoking during pregnancy, maternal birth

country and parental SES at birth. Life-limiting condition was modelled as a time-varying variable.

We estimated the time-varying effects (HRs) of the exposure in a smooth way by fitting flexible parametric models, with restricted cubic splines (5 df) to model the log baseline cumulative hazard function and 3 df to model the interaction between age and the exposure variable, where asthma and life-limiting conditions were time-varying variables, and the model was adjusted for all the covariates.²⁶

Effect modification by life-limiting conditions or parental SES was tested, using Wald test, by introducing an interaction term in the adjusted Cox proportional hazard model between asthma and (1) life-limiting conditions and (2) parental SES at birth.

From 2001 outpatient specialist visits are also available in the NPR. Hence data available from this year are thought to be more complete and could decrease the chance of misclassification bias of the asthma variable. In order to study the effect of this, a subgroup analysis was conducted on those born from 2000. They were studied by similar methods until 31 December 2013.

All statistical analyses were conducted using STATA V.15.1.

RESULTS

In total 261 322 asthma cases were identified, resulting in a cumulative incidence of asthma of 9.4%. Table 1 shows the characteristics of the study cohort and their family. The mean age of asthma onset was 8.1 years (95%CI 8.0 to 8.1). Asthma cases were more likely to be male, born premature or have been exposed to maternal smoking in pregnancy. Of those with asthma, 6480 individuals (cumulative incidence 2.5%) had a lifelimiting condition, and of those without asthma 28 798 individuals (cumulative incidence 1.1%) had a life-limiting condition.

Data on parental SES were available for 95.2% of the cohort. Of those with asthma, 17.9% of parents were in the lowest income quintile compared with those without asthma, where 19.4% of parents were in the lowest quintile. The distribution of parental education for the asthma group showed 5.9% had only compulsory schooling compared with the non-asthma group, where 6.4% had only compulsory schooling. Patterns of missing data of the variables prematurity, SGA and maternal smoking in pregnancy were studied across the parental SES variables. We found no increase in missing data among these groups; therefore, this should not cause bias in the analysis (data not supplied).

Outcome data

The mean follow-up time was 13.7 years (7.8 SD). There were 6592 individuals who died between 1 and 25 years of age, which is 0.2% of the cohort. The crude mortality rate was 18.1 (95% CI 17.6 to 18.5) per 100 000 person years. The unadjusted all-cause mortality rate for asthma cases was 32.1 (95% CI 29.5 to 34.9) per 100 000 person years, which was greater than for nonasthma cases at 17.4 (95% CI 17.0 to 17.8) per 100 000 person years (table 2).

Among those who died, 548 (8.3%) individuals had asthma and 970 (14.7%) individuals had a life-limiting condition. In total there were only 10 deaths where asthma was the leading cause of death (0.15% of all deaths). Of the study individuals who died during follow-up, 24.8% had parents in the lowest income quintile at birth compared with those who did not die during follow-up, where 19.2% had parents in the lowest income quintile at birth. The distribution of parental education at birth among those who died showed that 10.3% of the individuals had parents with only compulsory schooling, compared with those study individuals who did not die during follow-up, where 6.4% had parents with only compulsory schooling (table 3 and online supplemental table S2).

Main results

From the Cox proportional hazard model, the resulting HR for all-cause mortality was 1.68 (95% CI 1.54 to 1.83) by comparing those with asthma with those without asthma. Adjusting for covariates altered the HR to 1.46 (95% CI 1.33 to 1.62). The HR for all-cause

Table 1 Background characteristics related to asthma in a Swedish cohort of 2 775 430 individuals

Characteristic	No asthma	Asthma
n (%)	2 514 108 (90.6)	261 322 (9.4)
Study individuals' characteristics		
Sex		
Male	1 277 846 (50.9)	147 383 (56.4)
Female	1 236 255 (49.2)	113 939 (43.6)
Prematurity		
Yes (≤ 37 weeks)	144 043 (5.7)	22 243 (8.5)
No (> 37 weeks)	2 382 811 (94.3)	239 079 (91.5)
Small for gestational age		
Yes	56 886 (2.2)	7145 (2.7)
No	2 382 811 (94.8)	245 453 (94.0)
Missing	74 411 (3.0)	8724 (3.3)
Life-limiting condition		
Yes	28 798 (1.1)	6480 (2.5)
No	2 485 310 (98.9)	254 842 (97.5)
Family characteristics		
Maternal age at delivery, years		
<20	52 249 (2.1)	5444 (2.1)
≥ 20 to <25	420 197 (16.7)	45 615 (17.4)
≥ 25 to <30	840 276 (33.4)	90 611 (34.6)
≥ 30 to <35	779 249 (31.0)	79 073 (30.3)
≥ 35 to <40	349 137 (13.8)	33 960 (13.0)
≥ 40	71 630 (2.9)	6486 (2.5)
Missing	1370 (0.1)	133 (0.1)
Maternal smoking during pregnancy		
Yes	356 193 (14.2)	39 347 (15.1)
No	2 016 479 (80.2)	206 644 (79.1)
Missing	141 436 (5.6)	15 331 (5.8)
Maternal country of birth		
Sweden	2 066 737 (82.2)	225 482 (86.3)
Denmark, Norway, Finland, Iceland	69 516 (2.8)	6600 (2.5)
Other	374 597 (14.9)	29 214 (11.2)
Missing	3258 (0.1)	26 (<0.1)
Parental income		
Lowest	486 986 (19.4)	46 634 (17.9)
Lower middle	481 091 (19.1)	51 179 (19.6)
Middle	480 864 (19.1)	51 918 (19.9)
Upper middle	480 520 (19.1)	51 276 (19.6)
Highest	483 183 (19.2)	48 684 (18.6)
Missing	101 464 (4.0)	11 631 (4.5)
Parental education		
Compulsory school	161 801 (6.4)	15 364 (5.9)
High school	1 132 088 (45.1)	125 046 (47.8)
College or further education	1 101 778 (43.8)	108 189 (41.4)
Missing	118 441 (4.7)	12 723 (4.9)

The table compares those who received a diagnosis of asthma during follow-up with those who did not receive a diagnosis of asthma during follow-up.

mortality varied by age as estimated from the adjusted flexible parametric survival model allowing for a timevarying effect. The largest HR was seen for deaths between 5 and 15 years of age (figure 1).

In persons with asthma and with and without a life-limiting condition, the adjusted hazard rate (adjHR) for all-cause mortality differed ($p=0.002$), demonstrating a significant interaction. Those with asthma and a life-limiting condition had an adjHR of 1.87 (95% CI 1.57 to 2.22), whereas in those with asthma and without a life-limiting condition the all-cause mortality rate remained increased but was lower in those with a life-limiting condition, with an adjHR of 1.33 (95% CI 1.18 to 1.50). There was no significant interaction for measures of parental SES (income, $p=0.55$; education, $p=0.83$). The adjHRs are further depicted in figure 2 (see also online supplemental table S3), which compares the HR within each parental socioeconomic group.

Subgroup analysis

The subgroup analysis of 1 312 844 individuals born from 2000 included 121 959 asthma cases (cumulative incidence of 9.2%). The adjusted Cox regression model showed an HR of 1.79 (95% CI 1.39 to 2.08).

Table 2 Number of deaths and mortality rates by asthma exposure in a Swedish cohort of 2 775 430 individuals

	All	No asthma	Asthma
n	6592	6044	548
Person years at risk	364.2	347.7	17.1
Mean follow-up time, years	13.7	13.7	14.6
Crude mortality rate (per 100 000 person years) (95% CI)	18.1 (17.6 to 18.5)	17.4 (17.0 to 17.8)	32.1 (29.5 to 34.9)

DISCUSSION

This population-based cohort study of 2 775 430 individuals supports the hypothesis that the all-cause mortality rate in children and young adults is higher in those with asthma compared with those without asthma. We expand these findings by showing that having a life-limiting condition altered the rate between the asthma and non-asthma groups, whereas parental SES at birth did not. Few studies have investigated the relationship between asthma and all-cause mortality in younger people. To our knowledge, this is the largest population study of children and young adults on this topic, and this study adds to our understanding of the research field.

Studies on adult populations have demonstrated that asthma increases all-cause mortality,^{7,8} and our study further demonstrates that this association is seen in children and young adults. The recent study from Fleming *et al*⁹ has shown an increased all-cause mortality in children with asthma and our subgroup analysis of children aged 1–14 years old shows a similar HR to this study. Furthermore we have demonstrated that the hazard rate for the association between asthma and all-cause mortality changes with age, with the highest rate ratio in children aged 5–15 years old. This observation has previously not been reported and warrants further exploration.

Asthma is known to be comorbid with other chronic conditions, including life-limiting conditions.^{15,27} Our results, perhaps unsurprisingly, suggest that for children and young adults with a life-limiting condition the association between asthma and all-cause mortality is higher than for those without a life-limiting condition; however, what is more interesting to note is that the association between asthma and all-cause mortality remains even for those not identified as having a life-limiting condition. Studies investigating adults with asthma have shown an increased all-cause mortality among adults with other underlying disease,²⁸ and others propose that airflow limitation (FEV₁) is an important component contributing to mortality.^{29,30} Perhaps the relationship between asthma and all-cause mortality is related to increased susceptibility to factors associated with asthma comorbidities, other chronic disease and/or reduced lung function, which could be explored in future research. There is overwhelming evidence that SES in childhood impacts not only health outcomes and mortality in childhood but also adulthood.^{31,32} Evidence of this can be seen in this study, as study individuals who died had a higher proportion of parents from the lowest socioeconomic groups at birth (lowest income quintile and compulsory schooling only) compared with those who survived. Studies in adults with asthma have demonstrated an increased risk of both all-cause mortality and asthma-specific mortality among those from the lowest SES group compared with the highest SES group.⁸ Although we could not demonstrate a significant difference in the association of asthma and all-cause mortality between parental SES groups, parental SES is an important confounder in the relationship between asthma and all-cause mortality.¹⁸

The Swedish healthcare system is often cited as a system with an established healthcare structure of community and hospital services with the linkage of several patient medical record sources. This creates the right environment for the management of persons with chronic conditions.^{5,18} Healthcare in Sweden is universal, access to emergency care is uniform, and prescriptions for medications during the study period were subsidised.

Despite this, the results of this study demonstrate an increased mortality rate among children and young adults with asthma, supporting the argument for the integrated management of chronic conditions in children and young adults and in particular in the treatment of asthma.

Strengths and limitations

A strength of this study is the large population base, which minimises selection bias and increases generalisability. The variables retrieved from the NPR and the Swedish Cause of Death Register have been shown to have a high positive predictive value, and similarly data pertaining to parental SES at birth were derived from registers which have been validated.^{23,25,33}

There are some limitations. First, the study population included only individuals born in Sweden. Although this creates a selection bias, as it does not include individuals who immigrate to Sweden, it minimises misclassification bias with regard to the asthma variable and data pertaining to the pregnancy, perinatal outcomes and parental SES, which are not available for persons who are not born in Sweden. Second, the asthma variable was created largely from hospital data and hence we may have found more serious asthma cases and missed milder cases. In order to overcome this bias and capture more individuals with asthma who are managed in primary care, we have used data from the Swedish PDR, which started in 2005.

Asthma cases were defined in accordance with a validation study which found a high positive predictive value for asthma defined using both the NPR and/or the PDR.¹¹ Furthermore the subgroup analysis of those born from 2000 indicates that potential bias from a misclassification of the asthma variable probably has limited impact on the findings, as we demonstrate that the increased all-cause mortality persists for those with asthma. Third, we did not have access in the NPR to all the life-limiting conditions defined by Fraser *et al*,¹⁶ which might result in a misclassification bias and might affect our estimates in our adjusted model. Finally, we had access to data on maternal smoking during pregnancy but no other information on exposure to tobacco smoke or individual smoking habits. Smoking has been demonstrated as a significant factor which increases all-cause mortality in adults with asthma and differs within socioeconomic groups.⁷ In 2007, 14% of the Swedish population smoked and around 7% of the population reported daily environmental smoke exposure.³⁴ Therefore, the bias from not having smoking data may be minimal; however, we cannot rule smoke exposure out altogether.

Future research on asthma and all-cause mortality in children and young adults should further explore the effect of smoking and smoke exposure on this association.

CONCLUSION AND IMPLICATIONS

To our knowledge this is the first study specifically examining the relationship between asthma and all-cause mortality in children and young adults. While this study shows that asthma is associated with an increased rate of death in children and young adults, the asthma-specific mortality is still relatively low. The HR comparing the mortality rate in the asthma and non-asthma groups was increased by also having a lifelimiting condition, whereas parental SES at birth did not alter the association between asthma and all-cause mortality. The study provides further evidence that those with asthma have an increased all-cause mortality, which has important clinical implications and strengthens the argument for continued research in this field.

Table 3 Characteristics comparing individuals who died or survived the follow-up period

Characteristic	No asthma	Asthma
n (%)	6592	2 768 838
Study individuals' characteristics		
Asthma		
Yes	548 (8.3)	260 774 (9.4)
No	6044 (91.7)	2 508 064 (90.6)
Sex		
Male	4079 (61.9)	1 421 150 (51.3)
Female	2513 (38.1)	1 347 681 (48.7)
Prematurity		
Yes (≤ 37 weeks)	715 (10.9)	165 571 (6.0)
No (> 37 weeks)	5877 (89.1)	2 603 267 (94.0)
Small for gestational age		
Yes	381 (6.2)	63 650 (2.3)
No	5966 (91.0)	2 622 298 (94.7)
Missing	258 (3.8)	82 890 (3.0)
Life-limiting condition		
Yes	970 (14.7)	34 308 (1.2)
No	5622 (85.3)	2 734 530 (98.8)
Family characteristics		
Maternal age at delivery, years		
< 20	253 (3.8)	57 440 (2.0)
≥ 20 to < 25	1539 (23.4)	464 273 (16.8)
≥ 25 to < 30	2235 (33.9)	928 652 (33.5)
≥ 30 to < 35	1674 (25.4)	856 648 (30.9)
≥ 35 to < 40	711 (10.8)	382 386 (13.8)
≥ 40	179 (2.7)	77 937 (2.8)
Missing	1 (< 0.1)	1502 (< 0.1)
Maternal smoking during pregnancy		
Yes	1669 (25.3)	393 871 (14.2)
No	4456 (67.6)	2 218 667 (80.1)
Missing	467 (7.1)	156 300 (5.6)
Maternal country of birth		
Sweden	5517 (83.7)	2 286 702 (82.6)
Denmark, Norway, Finland, Iceland	294 (4.5)	75 822 (2.7)
Other	780 (11.8)	403 031 (14.6)
Missing	1 (< 0.1)	3283 (0.12)
Parental income		
Lowest	1637 (24.8)	531 983 (19.2)
Lower middle	1294 (19.6)	530 976 (19.2)
Middle	1218 (18.4)	531 564 (19.2)
Upper middle	1122 (17.0)	530 674 (19.2)
Highest	1093 (16.6)	530 774 (19.2)
Missing	228 (3.6)	112 867 (4.08)
Parental education		
Compulsory school	680 (10.3)	176 485 (6.4)
High school	3659 (55.5)	1 253 475 (45.3)
College or further education	1987 (30.1)	1 207 980 (43.6)
Missing	266 (4.1)	130 898 (4.7)

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Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information. No additional data available.

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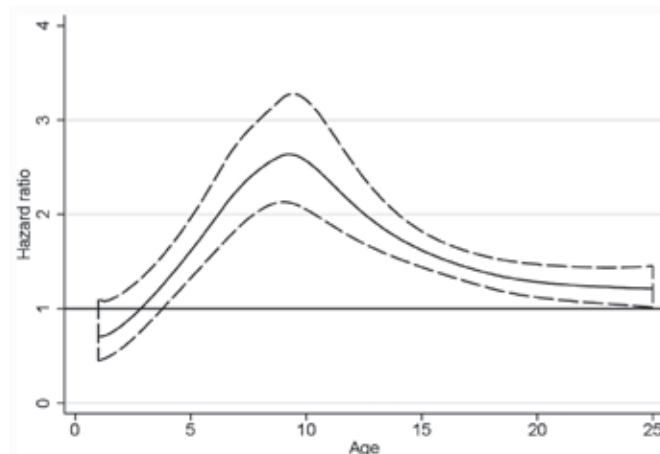


Figure 1 HR with 95% CI comparing all-cause mortality in Swedish individuals aged between 1 and 25 years of age with asthma and those without asthma. HR estimated from the adjusted flexible parametric model.

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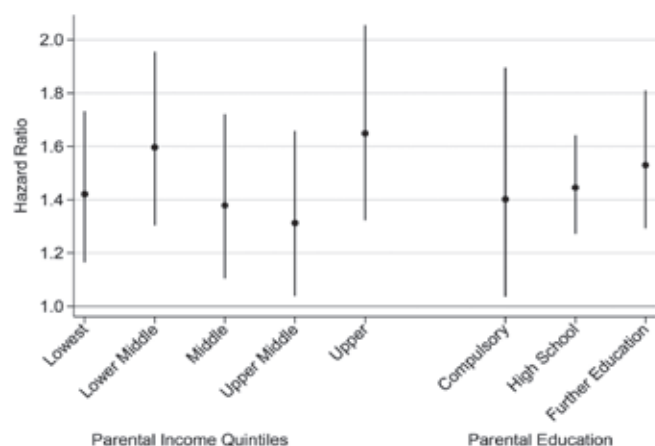


Figure 2 Adjusted HR with 95% CI estimated from Cox proportional hazards models of all-cause mortality comparing individuals with asthma and those without asthma within each parental socioeconomic group.

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INFORMAÇÕES ESSENCIAIS COMPATÍVEIS COM RESUMO DAS CARACTERÍSTICAS DO MEDICAMENTO

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ARTIGO ORIGINAL INVESTIGAÇÃO

O que os doentes consideram mais importante na escolha do tratamento para asma ligeira a moderada? Resultados de uma experiência de escolha discreta

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RESUMO

Contexto Recentemente, foi introduzido um regime de prevenção e alívio combinado (conforme necessário) como alternativa ao tratamento de prevenção diária convencional para a asma ligeira. Numa análise de subgrupo do estudo PRACTICAL, um ensaio pragmático, aleatorizado e controlado de terapia de alívio com budesonida-formoterol, *versus* terapêutica de alívio de manutenção com budesonida-terbutalina em adultos com asma ligeira, reportámos recentemente que cerca de dois terços preferiram uma terapêutica combinada de prevenção e de alívio conforme necessário. O objetivo deste estudo foi determinar a importância relativa dos atributos associados a estas duas terapêuticas da asma neste subgrupo de participantes que indicaram o seu tratamento preferido no estudo PRACTICAL.

Métodos Na consulta final do estudo, um subgrupo de participantes indicou o seu tratamento preferido e completou uma experiência de escolha discreta utilizando o método “*Potentially All Pairwise Rankings of all possible Alternatives*” e o software *1000minds*. Os atributos de tratamento e os seus níveis foram selecionados a partir de resultados de estudo mensuráveis e incluíram: regime de tratamento, falta de ar, dose de esteróides e probabilidade de ocorrência de crises de asma.

Resultados O conjunto de dados da análise final incluiu 288 participantes, 64% dos quais preferiram uma combinação de tratamento de prevenção e alívio conforme necessário. Entre os atributos, a “ausência de falta de ar” esteve no topo da classificação e o “risco mais baixo de crise de asma” ficou na segunda posição. Contudo, a importância relativa dos outros dois atributos variou em função da terapêutica preferida: o regime de tratamento recebeu uma classificação mais elevada pelos participantes que preferiam o tratamento “conforme necessário” *versus* os participantes que preferiam o tratamento de manutenção.

Conclusões O conhecimento das preferências dos doentes pelos atributos do tratamento, em conjunto com as características do regime terapêutico, pode ser utilizado na tomada de decisão partilhada relativamente à escolha do tratamento para doentes com asma ligeira a moderada.

Número de registo do ensaio ACTRN12616000377437.

INTRODUCTION

Symptom-driven inhaled corticosteroid (ICS)-formoterol represents a new paradigm in the treatment of mild asthma. This regimen has been shown to be safe and efficacious in four randomised controlled trials (RCTs)^{1–4} and was included in the 2019 update of the Global Initiative for Asthma (GINA) strategy framework^{5,6} as the preferred option at step 1 and as an alternative to low-dose maintenance ICS at step 2.

We have previously reported the results of a survey of patients with mild–moderate asthma who were completing an RCT comparing budesonide–formoterol reliever versus maintenance budesonide plus terbutaline reliever,⁴ asking them to choose between combination preventer and reliever therapy as-needed or twice-daily preventer with reliever as needed. About two-thirds of

Key messages

What is the key question?

► What are the most important features or ‘attributes’ of asthma treatments to patients when choosing between a new combination symptom-driven inhaled corticosteroid-reliever regimen and a conventional maintenance inhaled corticosteroid regimen with separate as-needed short-acting beta₂-agonist?

What is the bottom line?

► In this discrete choice experiment, the most important attribute of asthma treatment was the amount of shortness of breath, whereas the relative importance of other attributes varied depending on whether the patient preferred symptom-driven or maintenance-inhaled corticosteroids.

Why read on?

► Knowledge of patient preferences for asthma treatment together with regimen characteristics may aid clinical decision-making.

patients overall stated that they preferred a combination preventer and reliever as needed.⁷ However, the strength of patient preferences and the tradeoffs they might be willing to make to obtain this therapy are not known. Such knowledge of patient preferences could be incorporated into shared decision making by patients and their doctors.

Discrete choice experiments (DCEs),⁸ a methodology from the social sciences for identifying participants’ stated preferences, are increasingly used to quantify patient preferences with respect to the relative importance of the factors underpinning demand for various health services.⁹ DCEs involve participants repeatedly choosing between alternative hypothetical configurations of the service under consideration in terms of its key features or ‘attributes’. Participants’ choices are analysed to estimate preference weights (often referred to as ‘part-worth utilities’ in the DCE literature) that represent the relative importance to participants of the service’s attributes.¹⁰

The objective of this study was to conduct a DCE to determine the relative strength of patient preferences for different aspects of asthma treatment, in the context of their preferred treatment regimen: symptom-driven ICS-formoterol or maintenance ICS plus short-acting beta₂-agonist (SABA) as needed, in a subgroup of patients with

mild–moderate asthma completing the PRACTICAL study, a real-world RCT of these two treatments.⁴

METHODS

Description of the PRACTICAL study

The PRACTICAL study was a 52-week open-label parallel group, multicentre, phase III RCT undertaken across New Zealand. The methods and results are reported elsewhere.^{4,11} Adults with mild–moderate asthma who were taking SABA for symptom relief either with or without low-to-medium dose ICS were eligible for inclusion. Use of additional controller medications, such as montelukast, was an exclusion criterion; full inclusion and exclusion criteria for the PRACTICAL study are provided in online supplementary table S1. Participants were randomised 1:1 to either: budesonide–formoterol Turbuhaler (Symbicort), 200/6 µg, one inhalation as needed for symptom relief; or budesonide Turbuhaler (Pulmicort), 200 µg, one inhalation two times a day with terbutaline Turbuhaler (Bricanyl), 250 µg, two inhalations as needed for symptom relief.

Participants

The DCE was conducted with a subset of participants from the PRACTICAL study. Participants who were due their final visit on or after 26 March 2018 at 6 of the 15 sites were eligible. Participants who had withdrawn from the study prior to this date but would have otherwise been eligible were contacted and asked if they would be willing to complete the DCE. Sample size was dictated by the number of potentially eligible participants (n=407).

Stated preference for treatment option

At the final study visit, consenting patients completed a survey on a computer at the study site, with an investigator present in the same room in case of technical issues. At the start of the survey, participants were shown a description of the two randomised treatments in the PRACTICAL study (online supplementary figure S1), and a sheet explaining how to complete the DCE and the rationale for doing it (online supplementary figure S2). Investigators were instructed not to assist participants and to refer them to the explanation sheets if they had any questions. The survey content and results have been reported previously.⁷ The final question of the survey asked participants to state which of the two treatment plans they preferred. This choice determined which of two configurations of the DCE the participant completed: the ‘as-needed-preference DCE’ or the ‘maintenance-preference DCE’. Participants completed the DCE immediately after the survey, on the same computer.

Selection of attributes and levels

The attributes included in the DCE, and the levels for each attribute (table 1), represented key features of the two treatment options. They were specified based on a review of the literature, expert consensus and in consultation with participants who had completed the PRACTICAL study before the DCE eligibility date. Eleven participants who had completed the PRACTICAL study attended one of three focus groups to explore the most important features of asthma and its management, with particular focus on factors that had been measured within the PRACTICAL study and how these could be translated into attributes and levels that would be meaningful to participants. The

same 11 participants pilot tested the DCE to check understanding, relevance of selected attributed and levels and time taken to complete the DCE, with particular care taken to check their agreement with the inherent ranking of attribute levels. Cognitive debriefing was used to enhance feedback. Based on this feedback, iterative changes to the wording of the DCE were made during the pilot phase to improve understanding. None of the pilot participants found the DCE to be difficult to understand or unduly burdensome.

Wording was refined during pilot testing, and understanding was checked. Further details are given in the online supplementary.

Discrete choice experiment

The DCE was based on the PAPRIKA method¹²—an acronym for Potentially All Pairwise Rankings of all possible Alternatives—as implemented by 1000minds software (www.1000minds.com). This method and software have been used in a wide range of health applications.^{13–17}

All DCE methodologies involve the participants being asked to choose between two or more hypothetical options which are defined by different combinations of the attributes’ levels included in the DCE. In the present context, the PAPRIKA method¹² involved each participant being asked a series of ‘tradeoff questions’, where each question invited them to choose their preferred asthma treatment from a pair of hypothetical treatments defined on just two attributes at a time. Each choice required the participant to confront a tradeoff between the two attributes included for the pair of treatments, where the two other attributes were assumed to be the same for both treatments. An example of a tradeoff question appears in figure 1.

Such questions (always involving a trade off between the attributes, two at a time) are repeated with different pairs of hypothetical treatments. Each time the participant answers a question—that is, ranked a pair of treatments (including potentially ranking them equally)—all other pairs of treatments that could be pairwise ranked by applying the logical property of ‘transitivity’ are identified and eliminated by the software. For example, as an illustration of transitivity, if a person prefers treatment X to treatment Y and Y to Z, then—by transitivity—X is also preferred to Z (and so is not asked about by the software).

Also, each time a person answers a question, the method adapts the selection of the next question based on all of their preceding answers (always one whose answer was not implied by earlier answers); thus, PAPRIKA is a type of adaptive DCE. This adaptivity combined with the above-mentioned elimination procedure based on transitivity minimises the number of questions the participant is asked while ensuring they have pairwise ranked all possible treatments defined on two attributes at a time, either explicitly or implicitly (by transitivity).

Finally, from the participant’s explicit pairwise rankings (ie, answers to the tradeoff questions), the software uses linear programming techniques to derive weights (‘part-worth utilities’) for the levels on each attribute.¹²

The values for the highest levels across the four attributes sum to 1, so each of these values represents the attribute’s relative weight overall. The lowest level of each attribute gets a value of zero. The values assigned to the middle level of an attribute represents the combined effect of the level’s middle position on the particular attribute as well as the attribute’s relative weight (as above). This representation of weights is equivalent to the more traditional

Table 1 Attributes and levels

Attribute	Participant’s stated ranking of levels, in as-needed preference DCE	Participant’s stated ranking of levels, in maintenance preference DCE
Type of asthma treatment	A preventer inhaler taken twice a day every day, with a reliever inhaler taken as needed A combined preventer and reliever inhaler, taken as needed	A combined preventer and reliever inhaler, taken as needed A preventer inhaler taken twice a day every day, with a reliever inhaler taken as needed
Attribute	Inherent ranking of levels, in as-needed-preference DCE	Inherent ranking of levels, in maintenance-preference DCE
The dose of your steroid inhaler	Medium Low Very low	Medium Low Very low
Likelihood of a flare-up in your asthma severe enough that you need to see a doctor	20 out of 100 people in a year (20%) 10 out of 100 people in a year (10%) 5 out of 100 people in a year (5%)	20 out of 100 people in a year (20%) 10 out of 100 people in a year (10%) 5 out of 100 people in a year (5%)
In an average week you will be short of breath because of asthma	A moderate amount or more A little Not at all	A moderate amount or more A little Not at all

Each attribute’s levels are presented within the table in increasing order of preference (ie, the lowest ranked level is listed first). DCE, discrete choice experiment.

Figure 1 Example of a tradeoff question from the 1000minds software.

nal approach where normalised attribute weights and single-attribute value scores are used; we used nonnormalised representation because it simplifies the presentation of results. Further details on the PAPRIKA method—in particular, the method by which the weights were derived are provided in the online supplementary appendix.

PAPRIKA's application of the transitivity property requires that each attribute's levels have an inherent ranking in terms of people's preferences,¹² that is, a ranking that would be universally accepted. For example, with respect to the attribute 'likelihood of a flare up', a 5% risk would be assumed to be universally preferred (higher ranked) relative to a 10% risk. In contrast, the two levels for the attribute 'treatment regimen' (ie, the two randomised treatments in the PRACTICAL study) do not have an inherent ranking because each person's ranking would depend on which therapy they preferred. Therefore, it was necessary to implement two separate DCEs, identical except that the ranking of the two levels for the 'treatment regimen' attribute were reversed. After each participant had indicated their preferred therapy, they were presented with the appropriate DCE for them. For participants who had stated they preferred the as-needed therapy this regimen was ranked above the maintenance regimen in their DCE, and vice versa.

The final specification for each DCE's attributes and levels is presented in table 1.

Data quality checks

The consistency of each participant's choices was tested by repeating two previously answered tradeoff questions at the end of the DCE. The time each participant took to answer each question was also recorded by the 1000minds software. Participants who answered both repeated questions inconsistently and/or answered their questions implausibly quickly (less than 4 seconds per question) were excluded from the final analysis.

Data analysis

Preference weights were calculated for each participant and were also averaged across all participants. Continuous variables are described by mean and SD or median and IQR. Categorical variables are described by counts and proportions as percentages.

RESULTS

Participants

Participant flow is shown in online supplementary figure S3. Of the 407 eligible patients, 306 recorded their preferred treatment and 296 (73%) started a DCE. Eight participants' DCEs were excluded: one because it was incomplete, and seven because the participant answered both repeated questions inconsistently. No participant answered their questions implausibly quickly. This gave a total of 288 DCEs in the final dataset. Overall, 185 participants (64%) preferred a combined preventer and reliever inhaler as needed and so completed the as-needed-preference DCE; 103 participants (36%) preferred a preventer inhaler taken two times a day every day, with a reliever inhaler taken as needed, and so completed the maintenance-preference DCE.

Participant characteristics are reported in table 2. As previously reported,⁷ study randomised treatment differed between the two groups, with participants more likely to express a preference for the randomised treatment they took during the study, particularly for those randomised to budesonide-formoterol as needed.

DCE results

For the DCEs, the median number of tradeoff questions answered by each participant was 13, with a mean time of 18.6 s per answer.

Mean preference weights for the attributes and levels and attribute ranking for the two DCEs are reported in table 3. For both DCEs, the highest ranking was given to 'shortness of breath in an average week' ('not at all'), with a weight of 0.33 (0.12) in the as-needed-preference DCE and 0.34 (0.12) in the maintenance-preference DCE. The second highest rank in both DCEs was for the lowest 'likelihood of an asthma flare-up', that is, 5 out of 100 people (5%) having a flare-up in a year.

For the as-needed-preference DCE, this 'likelihood of asthma flare up' had a similar mean weight as an as-needed 'treatment regimen': 0.25 (0.09) and 0.24 (0.11) respectively. 'Dose of steroid' was the lowest ranked attribute, with a weight of 0.17 (0.11) for 'very low' dose. For the maintenance-preference DCE, the level of 5 out of 100 people for 'likelihood of asthma flare up' was ranked second, with a weight of 0.30 (0.12). 'Very low' dose of steroid was ranked third and the maintenance 'treatment regimen' ranked fourth; however, they had similar weights: 0.19 (0.10) and 0.18 (0.12), respectively. For both DCEs, there was evidence of variability in preferences for each attribute as indicated by the SD. Mean preference weights within each DCE were similar irrespective of randomised treatment (online supplementary tables S4 and S5).

DISCUSSION

In patients with mild-moderate asthma completing a pragmatic open-label study of two treatments, this study has shown for an average week being short of breath 'not at all' had the greatest influence on patient preferences for an asthma treatment, out of the treatment attributes and levels included in a DCE. However, the influence on patient preferences for levels of the other three attributes included in our DCEs differed depending on whether participants, prior to starting the DCE, stated that they preferred a combined preventer and reliever inhaler taken as needed, or a preventer inhaler taken two times a day every day with a reliever inhaler taken as needed. Though a lower likelihood of an asthma flare-up was ranked second in both DCEs, for those who preferred combined treatment taken as needed, this regimen and a lower likelihood of an asthma flare-up had similar preference weights, indicating that they were of similar importance. A very low 'dose of steroid' was the lowest ranked attribute, indicating that it was the least important. In contrast, for participants who preferred maintenance treatment two times a day, this regimen and very low 'dose of steroid' were of similar weight and the least important attributes.

For both DCEs, the mean preference weights were similar irrespective of the patients' randomised treatment group (the treatment group that they were randomised to, not necessarily the one that they preferred), suggesting that strength of preference for the attribute levels associated with a particular regimen was not determined by prior experience of that regimen during the RCT (online supplementary tables S4 and S5). This finding contrasts with the preference for the specific regimen, which we have previously reported was strongly determined by the randomised treatments received by the participants⁷: 90% of patients randomised to budesonide-formoterol preferred as-needed treatment, and 60% of those randomised to maintenance budesonide-preferred maintenance treatment.

Our results are consistent with other DCEs completed by patients with asthma using different DCE methods, which found attributes that represent more shortness of breath or higher symptom frequency are the most important attributes.^{18–19} Similar to other DCE studies,^{20–21} reduced risk of asthma exacerbations and flare-ups were also important, ranking second in this population with mild-moderate asthma. Other DCEs report conflicting results with respect to the importance of ICS dose.^{19–22} No previous DCEs included an as-needed asthma regimen as an attribute, but previous studies found that patients prefer regimens with fewer inhalers^{21–23} or that are convenient to use and have a lower dosing frequency.²⁰

Patient preferences for different attributes of asthma treatment may help determine which regimen is most suitable for them. The PRACTICAL study⁴ reported no difference between the treatment regimens in asthma symptoms as assessed by the group mean Asthma Control Questionnaire-5. However, the Symbicort Given as-needed in Mild Asthma (SYGMA) 1 and 2^{1,2} and Novel Symbicort Turbuhaler Asthma Reliever Therapy (START)³ studies reported a slightly higher level of asthma symptoms with as-needed budesonide-formoterol compared with maintenance budesonide. Although

Table 2 Participant characteristics by their preferred treatment therapy*, which determined which of the two discrete choice experiments (DCEs) they completed

Characteristic	Preferred therapy, chosen before the DCE	
	As-needed combination preventer and reliever, n=185	Twice-daily maintenance treatment, n=103
Randomised treatment		
Budesonide–formoterol, n (%)	125 (68)	14 (14)
Maintenance budesonide, n (%)	60 (32)	89 (86)
Baseline variables		
Age (year)	44.2 (15.3)	47.6 (17.8)
Female sex, n (%)	104 (56)	59 (57)
Ethnicity, n (%)		
Asian	8 (4)	8 (8)
NZ European	145 (78)	88 (85)
Māori	18 (10)	3 (3)
Other	3 (2)	2 (2)
Pacific	11 (6)	2 (2)
Smoking status, n (%)		
Current smokers	11 (6)	1 (1)
Ex-smokers	47 (25)	29 (28)
Never smokers	127 (69)	73 (71)
Pack years (among ever smokers)	5.5 (4.7) n=58	5.2 (5.4) n=30
Age at diagnosis (year)	19.1 (18.4)	24.1 (20.9)
Self-reported ICS use in 12 weeks prior to randomisation, n. (%)†	122 (66)	79 (77)
Self-reported ICS adherence (%)	54.3 (36.7) n=122	61.7 (33.5) n=79
Self-reported ICS use ever, n (%)	158 (85)	90 (87)
End-of-study variables		
Final visit ACQ-5‡	0.82 (0.70)	0.64 (0.69)
Final visit on treatment FEV ₁ % of predicted value§	89.9 (15.0)	88.7 (15.6)
Final visit median Fe _{NO} , ppb (IQR)	22 (15–38)	23 (15–40)
Participants experiencing ≥1 exacerbation or severe exacerbation during the study, n (%)	25 (14)	19 (18)
Number of severe exacerbations during the study, n (%)		
0	160 (86)	84 (82)
1	18 (10)	17 (17)
2	6 (3)	2 (2)
3	1 (1)	0
Early withdrawal, n (%)	8 (4)	11 (11)

Values are expressed as means (SD), unless otherwise stated.

*Participants were asked 'Which of the following asthma treatment plans would you prefer?' with the options of either 'A preventer inhaler taken twice a day every day, with a reliever inhaler taken as needed' or 'A combined preventer and reliever inhaler taken as needed'. Depending on their answer they were directed to the as-needed-preference DCE or the maintenance-preference DCE.

†Patient-reported adherence to inhaled corticosteroid (ICS) in the 4 weeks prior to enrolment (% prescribed dose).

‡The Asthma Control Questionnaire-5 (ACQ-5) consists of five questions that assess asthma symptoms in the previous week, each of which is scored on a 7-point scale that ranges from 0 (no impairment) to 6 (maximum impairment), and averaged, in which a 0.5-unit change represents the minimal clinically important difference.

§Participants received no instruction to withhold their bronchodilator before measurement of FEV₁.³³ ppb, parts per billion; SABA, short-acting beta₂-agonist.

in all three studies, this was well below the minimal clinically important difference. Though either regimen may be suitable for a patient who wishes to avoid breathlessness, the results of these four studies considered together suggest that maintenance budesonide may be more appropriate for patients who have a strong preference to avoid symptoms. The lower rate of severe exacerbations with as-needed budesonide–formoterol compared with maintenance budesonide in the PRACTICAL and Novel START studies^{3,4} and similar rates between the two regimens in the SYGMA studies^{1,2} suggests that as-needed budesonide–formoterol may be more appropriate for those at risk of exacerbations, or who are concerned about exacerbations. Exposure to ICS was significantly lower in the as-needed budesonide–formoterol group in all four studies. Therefore, as-needed budesonide–formoterol may be more appropriate for patients who wish to limit their exposure to ICS. Understanding patient preferences and priorities for asthma treatment is important when discussing management options with patients, particularly as as-needed budesonide–formoterol enters clinical practice.

As with any DCE, hypothetical bias and different interpretations of the attributes and levels between participants may have affected the results.²⁴ We attempted to mitigate this risk by only including attributes and levels that were realistic and relatable. Shortness of breath was the only symptom included in the DCE, whereas asthma also causes wheeze, cough and night waking. During pilot testing, the attribute 'dose of steroid' and its associated levels were interpreted as reflecting different levels of exposure to ICS, rather than specific levels of risk of side effects. Prior to completing the DCE, participants were aware of both treatment regimens—from personal experience in the case of their own randomised treatment, and from information provided at the start of the PRACTICAL study and at the last visit for the other treatment. To limit cognitive burden and the number of questions in the DCE, we opted to include only four attributes which were considered to be the important influencers of choice, but other attributes such as side effects or asthma-related healthcare costs¹⁹ may also be relevant. However, for both DCEs, the levels of all four attributes influenced participants' choices.

Other potential limitations include the fact that participants were asked to choose between hypothetical asthma treatments defined on levels of just two attributes at a time. Therefore, participants were not making each choice based on the full set of four attributes, and so our results may be susceptible to bias as participants may have been choosing based on assumptions about the other two attributes.^{25,26} However, the use of partial profiles can help mitigate effects of attribute dominance and reduces the complexity of choices for the participant.²⁷ In addition, the maintenance regimen offered in the DCE-specified twice-daily treatment, as studied in PRACTICAL; however, several ICS formulations are approved for once-daily use, and specifying twice-daily treatment for the regimen attribute may have biased preferences towards the as-needed regimen. Reading ability was not specifically evaluated, but prior to starting the DCE, participants had already completed the consent form and the preferences survey, as well as questionnaires at each visit of the RCT itself.

As the categorical attribute of regimen preference did not have an inherent ranking (ie, that was universally accepted), we developed two almost identical DCEs in order to use the PAPRIKA method and obtain preference weights for each individual participant. As this study was conducted in participants completing an RCT, the sample may not be representative of the general mild-moderate asthma population, who would be eligible for as-needed treatment, but may have different preferences and priorities. Previous population-based studies conducted in patients with asthma have found patients prefer regimens that are less intrusive²⁸ and to increase their reliever inhalers over their preventer inhalers even in response to worsening asthma symptoms.²⁹

A DCE was not completed by 112 eligible participants (28%). On review of their characteristics (online supplementary table S6), there was a higher early withdrawal rate and their preferences may be different from those who completed a DCE. There were 19 participants who withdrew early and completed a DCE. Of these, those who completed the maintenance-preference DCE had a higher preference weight for the lowest likelihood of an asthma flare-up, whereas those who completed the as-needed-preference DCE had a higher weight for dose of steroid compared with the whole group (online supplementary table S7).

This study is the first to investigate patient preferences for two specific asthma therapies using DCE methodology. Previous DCEs have explored patient preferences for attributes of asthma treatment,^{20–22,30,31} but this is the first DCE to have compared a regular versus an as-needed preventer therapy. This is highly relevant as symptom-driven ICS formoterol is a new treatment which was included in the 2019 GINA update at steps 1 and 2, and has been approved by regulators in multiple countries. Understanding patient preferences and priorities for their asthma treatment is important when discussing management options with patients. Previous qualitative studies have shown that patients can have a strong attachment to their SABA reliever inhalers,³² which may have implications when switching to a new reliever medication. However, in a survey of patient preferences for, and experiences of, as-needed budesonide–formoterol also conducted in this subgroup of participants,⁷ we found that 92% of those who were randomised to as-needed budesonide–formoterol were confident in using it as a reliever inhaler by the end of the study. This finding suggests that after an opportunity to try low-dose budesonide–formoterol as reliever therapy, most patients will find it an acceptable strategy. However, we cannot assume that the results of this analysis, conducted among clinical trial participants, are generalisable to the wider population of people with asthma. The priority now is to explore attitudes and barriers to budeso-

Table 3 Mean preference weights and ranking for the attributes and levels in each discrete choice experiment (DCE)

Attribute	Level	Mean weight (SD)	Attribute rank
As-needed-preference DCE, n=185			
Treatment regimen	A preventer inhaler taken two times a day every day, with a reliever inhaler taken as needed	0	
	A combined preventer and reliever inhaler, taken as needed	0.24 (0.11)	3
Dose of steroid	Medium	0	
	Low	0.10 (0.08)	
	Very low	0.17 (0.11)	4
Likelihood of asthma flare-up severe enough to need to see your doctor	20 out of 100 people in a year (20%)	0	
	10 out of 100 people in a year (10%)	0.14 (0.07)	
	5 out of 100 people in a year (5%)	0.25 (0.09)	2
Shortness of breath in an average week	A moderate amount or more	0	
	A little	0.20 (0.09)	
	Not at all	0.33 (0.12)	1
Maintenance-preference DCE, n=103			
Treatment regimen	A combined preventer and reliever inhaler, taken as needed	0	
	A preventer inhaler taken twice a day every day, with a reliever inhaler taken as needed	0.18 (0.12)	4
Dose of steroid	Medium	0	
	Low	0.11 (0.08)	
	Very low	0.19 (0.10)	3
Likelihood of asthma flare-up severe enough to need to see your doctor	20 out of 100 people in a year (20%)	0	
	10 out of 100 people in a year (10%)	0.16 (0.08)	
	5 out of 100 people in a year (5%)	0.30 (0.12)	2
Shortness of breath in an average week	A moderate amount or more	0	
	A little	0.19 (0.09)	
	Not at all	0.34 (0.12)	1

Bold values represent the relative weights of the attributes overall (ie, these bold values sum to 1, subject to rounding).

nide-formoterol reliever therapy in the general asthma population and the perspective of prescribers to this new approach to reliever therapy.

Strengths of our study include that we have incorporated investigation of patient preferences for attributes of asthma regimens into an RCT. This study was independent of the pharmaceutical industry and was independently funded. That we asked participants to state their preference for one of the two regimens prior to commencing the DCE means that preference weights for attribute levels are directly related to their preferred treatment regimen.

In conclusion, we investigated the relative importance to patients of different levels of four attributes of symptom-driven combination preventer and reliever or of maintenance preventer with symptom-driven reliever regimens, and related those preferences back to data measured in an RCT. Our results suggest that no shortness of breath and low likelihood of asthma flare-up were the two most important attributes. However, the patient's preferred regimen influenced their preference for likelihood of a flare-up, steroid dose and treatment regimen. Knowledge of patient preferences for treatment attributes together with knowledge of regimen characteristics could be used in discussion with patients to determine the most appropriate regimen for them, based on their preferences for regimen, shortness of breath, likelihood of an asthma flare-up and steroid dose.

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Contributors CB, PH, RJH, RB, HKR and JF conceived the idea and designed the study. CB, JKH and JS collected the data. MH monitored the study and undertook data management. CB, JF and MW undertook data analysis. All authors had access to analyses of study data. CB and PH wrote the first draft of the manuscript, and all authors contributed to and approved the final version.

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Competing interests CB reports personal fees from AstraZeneca and Novartis. PH co-owns and co-created the 1000minds software used in this study, which was created for the purpose of supporting elements of the methodology explained herein and which is made available to many academics (to date, more than 2000 researchers and students worldwide), including for the present study for free. RJH reports grants from AstraZeneca and Boehringer Ingelheim; and personal fees from Menarini. JKH reports personal fees from AstraZeneca. RB reports grants from Genentech, AstraZeneca, GlaxoSmithKline; and personal fees from AstraZeneca and Theravance. HKR reports grants from AstraZeneca and Novartis; personal fees from AstraZeneca, GlaxoSmithKline, Merck, Novartis, Teva, Mundipharma, and Boehringer Ingelheim; and is chair of the Global Initiative for Asthma scientific committee. JF reports grants from AstraZeneca, GlaxoSmithKline, and Genentech; and personal fees and non-financial support from AstraZeneca and Boehringer Ingelheim.

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Data availability statement Data are available upon reasonable request. Deidentified individual participant DCE data from the PRACTICAL trial will be shared beginning two years after article publication with no end date. These data will be available to researchers who provide a methodologically sound proposal for the purposes of achieving specific aims outlined in that proposal. Proposals should be directed to Richard Beasley via email: richard.beasley@mrnz.ac.nz and will be reviewed by the PRACTICAL study management committee. Requests to access data to undertake hypothesis-driven research will not be unreasonably withheld. To gain access, data requesters will need to sign a data access agreement and to confirm that data will only be used for the agreed purpose for which access was granted.

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1) Woodcock A et al. *Lancet* 2017; 390:2247-2255. 2) Bateman ED et al. *Thorax* 2014; 69:312-319. 3) GINA. Global strategy for asthma management and prevention, 2019. Available at: <https://ginasthma.org/gina-reports/> (Acedido: março 2020). 4) Vestbo J et al. *Lancet* 2016;387:1817-1826. ICS: Corticosteroide inalado; LABA: Agonista β_2 de longa duração.

INFORMAÇÕES ESSENCIAIS COMPATÍVEIS COM O RCM • NOME DO MEDICAMENTO Revinty Ellipta **COMPOSIÇÃO QUALITATIVA E QUANTITATIVA** Revinty Ellipta 92/22 mcg: Cada inalação disponibiliza uma dose administrada de 92 mcg de furoato de fluticasona e 22 mcg de vilanterol (como trifenatato). Isto corresponde a um recipiente unidose de 100 mcg de furoato de fluticasona e 25 mcg de vilanterol (como trifenatato). Revinty Ellipta 184/22 mcg: Cada inalação disponibiliza uma dose administrada de 184 mcg de furoato de fluticasona e 22 mcg de vilanterol (como trifenatato). Isto corresponde a um recipiente unidose de 200 mcg de furoato de fluticasona e 25 mcg de vilanterol (como trifenatato). **FORMA FARMACÊUTICA** Pó para inalação em recipiente unidose **INDICAÇÕES TERAPÊUTICAS** Asma: Revinty Ellipta 92/22 mcg e 184/22 mcg está indicado para o tratamento regular da asma em adultos e adolescentes com idade ≥ 12 anos em que a utilização de um medicamento contendo uma associação (agonista beta2 de ação prolongada e corticosteroides para inalação) é adequada: doentes que não estão adequadamente controlados com corticosteroides para inalação e com agonistas beta2 de curta duração de ação conforme o necessário; doentes que estão já adequadamente controlados com corticosteroide para inalação e agonista beta2 de longa duração de ação. **DPOC:** Revinty Ellipta 92/22 mcg está indicado para o tratamento sintomático de adultos com DPOC com um FEV1 previsível normal $<70\%$ (após o broncodilatador) com antecedentes de exacerbação apesar da terapêutica regular com um broncodilatador. **POSOLOGIA E MODO DE ADMINISTRAÇÃO** Asma (92/22 mcg e 184/22 mcg) Adultos e adolescentes ≥ 12 anos Deve considerar-se uma dose inicial de uma inalação de 92/22 mcg uma vez por dia para adultos e adolescentes ≥ 12 anos que requeiram uma dose média de corticosteroides para inalação em associação com um agonista beta2 de ação prolongada. Se os doentes não estiverem corretamente controlados com 92/22 mcg, a dose pode ser aumentada para 184/22 mcg. Os doentes devem ser regularmente reavaliados. A dose deve ser titulada para a dose mais baixa com a qual é mantido um controlo efetivo dos sintomas. Revinty Ellipta 184/22 mcg deve ser considerado para adultos e adolescentes ≥ 12 anos que requeiram uma dose mais elevada de corticosteroides para inalação em associação com um agonista beta2 de ação prolongada. Os doentes normalmente verificam uma melhoria na função pulmonar 15 minutos após a inalação. É necessário o uso diário regular para manter o controlo dos sintomas de asma e o uso deve ser continuado mesmo quando esta é assintomática. Se os sintomas surgirem no período entre as doses, deve ser tomado um agonista beta2 de curta duração, por inalação, para o alívio imediato. A dose máxima recomendada é 184/22 mcg 1x/dia. Crianças <12 anos A segurança e a eficácia ainda não foram estabelecidas na indicação para a asma. **DPOC (92/22 mcg)** Adultos ≥ 18 anos Uma inalação 1x/dia. Os doentes normalmente verificam uma melhoria na função pulmonar 16-17 minutos após a inalação. **População pediátrica** Não é relevante na população pediátrica para a indicação de DPOC. **Populações especiais** Idosos (> 65 anos) e Compromisso renal Não é necessário ajustar a posologia. **Compromisso hepático** Estudos revelaram um aumento na exposição sistémica ao FF. Devem tomar-se precauções na definição da posologia em doentes com compromisso hepático que possam estar em risco mais elevado de reações adversas sistémicas associadas a corticosteroides. Para os doentes com compromisso hepático moderado ou grave a dose máxima é 92/22 mcg. **Modo de administração** Via inalatória. Deve ser administrado à mesma hora do dia, todos os dias. Se uma dose for omitida, deve tomar-se a próxima dose à hora habitual no dia seguinte. Após inalação, os doentes devem enxaguar a boca com água sem a engolir. **CONTRAINDICAÇÕES** Hipersensibilidade às substâncias ativas ou a qualquer um dos excipientes. **ADVERTÊNCIAS E PRECAUÇÕES ESPECIAIS DE UTILIZAÇÃO** **Deterioração da doença** Não deve ser utilizado para tratar sintomas de asma aguda ou uma exacerbação aguda na DPOC, para os quais é necessário um broncodilatador de curta duração. O uso aumentado de broncodilatores de curta duração para aliviar os sintomas indica deterioração do controlo. Os doentes não devem interromper a terapêutica na asma ou na DPOC, sem supervisão de um médico, uma vez que os sintomas podem reaparecer após a descontinuação. Os acontecimentos adversos e as exacerbações relacionadas com a asma podem ocorrer durante o tratamento. Deve pedir-se aos doentes que continuem o tratamento mas que procurem aconselhamento médico se os sintomas da asma continuarem incontroláveis ou piorarem após o início do tratamento com Revinty Ellipta. **Broncospasmo paradoxal** Pode ocorrer com um aumento imediato na pieira após a administração. Deve ser tratado imediatamente com um broncodilatador para inalação de curta duração. Revinty Ellipta deve ser suspenso imediatamente, o doente avaliado e uma terapêutica alternativa instituída conforme o necessário. **Efeitos cardiovasculares** Podem ser observados efeitos cardiovasculares, tais como arritmias cardíacas por ex., taquicardia supraventricular e extra-sístoles. Num estudo controlado com placebo em indivíduos com DPOC moderada e com antecedentes, ou um risco aumentado de doença cardiovascular, não existiu aumento do risco de acontecimentos cardiovasculares. No entanto, deve ser utilizado com precaução em doentes com doença cardiovascular grave ou anomalias do ritmo cardíaco, tireotoxicose, hipocalcemia não corrigida ou em doentes com predisposição para níveis baixos de potássio sérico. **Doentes com compromisso hepático** Para os doentes com compromisso hepático moderado a grave, deve ser utilizada a dose de 92/22 mcg. **Efeitos sistémicos dos corticosteroides** Podem ocorrer com qualquer corticosteroide para inalação, em especial com doses elevadas receitadas durante longos períodos (ocorrência muito menos provável do que com corticosteroides orais). Incluem síndrome de Cushing, características cushingoides, apoplexia suprarrenal, diminuição na densidade mineral óssea, retardação do crescimento em crianças e adolescentes, cataratas e glaucoma e, mais raramente, uma variedade de efeitos psicológicos e comportamentais incluindo hiperatividade psicomotora, perturbações do sono, ansiedade, depressão ou agressão (em especial em crianças). Administrar com precaução em doentes com tuberculose pulmonar ou em doentes com infeções crónicas ou não tratadas. **Perturbações visuais** Podem ser notificadas perturbações visuais com o uso sistémico e tópico de corticosteroides. Se um doente apresentar sintomas tais como visão turva ou outras perturbações visuais, o doente deve ser considerado para encaminhamento para um oftalmologista para avaliação de possíveis causas que podem incluir cataratas, glaucoma ou doenças raras, como coriorretinopatia serosa central (CRSC), que foram notificadas após o uso de corticosteroides sistémicos e tópicos. **Hiperlipcemia** Notificados casos de aumentos nos níveis de glucose no sangue em doentes diabéticos e tal deve ser considerado quando se receita a doentes com antecedentes de diabetes mellitus. **Pneumonia em doentes com DPOC** Um aumento da incidência de pneumonia, incluindo pneumonia que requer hospitalização, tem sido observado nos doentes com DPOC a receberem corticosteroides inalados. Existe alguma evidência de um risco aumentado de pneumonia com o aumento da dose de esteroide mas isto não foi demonstrado de forma conclusiva entre todos os 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, índice de massa corporal (IMC) baixo e DPOC grave. **Pneumonia em doentes com asma** A incidência de pneumonia em doentes com asma foi frequente na dose mais elevada. A incidência de pneumonia em doentes com asma a tomar 184/22 mcg foi numericamente superior quando comparada com aqueles a receber 92/22 mcg ou placebo. Não foram identificados fatores de risco. **Excipientes** Cada dose administrada contém aproximadamente 25 mg de lactose (na forma mono-hidratada). Doentes com problemas hereditários raros de intolerância à galactose, deficiência total de lactase ou malabsorção de glucose-galactose não devem utilizar este medicamento. **EFEITOS INDESEJÁVEIS** As reações adversas mais frequentemente notificadas foram cefaleia e nasofaringite. Com a exceção de pneumonia e fraturas, o perfil de segurança foi semelhante em doentes com asma e DPOC. Durante os estudos clínicos, pneumonia e fraturas foram mais frequentemente observadas em doentes com DPOC. **Infeções e infeções** Frequentes Pneumonia, infeção do trato respiratório superior, bronquite, gripe, candidase da boca e da garganta. **Doenças do sistema imunitário** Raras Reações de hipersensibilidade incluindo anafilaxia, angioedema, erupção cutânea e urticária. **Perturbações do foro psiquiátrico** Raras Ansiedade. **Doenças do sistema nervoso** Muito frequentes Cefaleia Raras Tremor. **Afeções oculares** Pouco frequentes Visão turva. **Doenças cardíacas** Pouco frequentes Extra-sístoles Raras Palpitações, taquicardia. **Doenças respiratórias, torácicas e do mediastino** Muito frequentes Nasofaringite Frequentes Dor orofaríngea, sinusite, faringite, rinite, tosse, disfonia Raras Broncospasmo paradoxal. **Doenças gastrointestinais** Frequentes Dor abdominal. **Afeções musculoesqueléticas e dos tecidos conjuntivos** Frequentes Artralgia, dorsalgia, fraturas, espasmos musculares. **Perturbações gerais e alterações no local de administração** Frequentes Pirexia. **TITULAR DA AIM** GlaxoSmithKline (Ireland) Limited, 12 Riverwalk, Citywest Business Campus, Dublin 24, Irlanda. **DATA DA REVISÃO DO TEXTO** dezembro 2018. **APRESENTAÇÃO:** Revinty Ellipta 92 mcg+22 mcg, 30 doses; Revinty Ellipta 184 mcg+22 mcg, 30 doses. **Regime de comparticipação:** Escalão B. Regime Geral 69%; Regime Especial 84%. **Medicamento Sujeito a Receita Médica.** Está disponível informação pormenorizada sobre este medicamento no sítio da internet da Agência Europeia de Medicamentos <http://www.ema.europa.eu/>. Consultar o RCM completo para informação detalhada. Para mais informações e em caso de suspeita de um acontecimento adverso ou de outra informação de segurança, contactar o departamento médico da GlaxoSmithKline - +351 214129500. Para mais informações contactar o representante local do titular da AIM: Bial-Portela & Cª, S.A., -A Av. da Siderurgia Nacional, 4745-457, S.Mamede do Coronado; NIF: 500220913; DDVSA190129

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ARTIGO ORIGINAL INVESTIGAÇÃO

Epidemiologia molecular e impacto clínico das infeções por rinovírus em adultos durante três estações epidémicas em 11 países europeus (2007-2010)

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RESUMO

Contexto As diferenças no impacto clínico entre espécies e tipos de rinovírus (RV) em adultos não estão bem definidas. O objetivo deste estudo foi determinar a epidemiologia e o impacto clínico das diferentes espécies de RV.

Métodos Realizámos um estudo prospetivo sobre infeções por RV em adultos com tosse aguda/infeção do trato respiratório inferior (ITRI) e controlos assintomáticos. Foram recrutados indivíduos de 16 redes de cuidados primários localizadas em 11 países europeus entre 2007 e 2010. A deteção e genotipagem de RV foi realizada por meio de ensaios de reação em cadeia da polimerase com transcriptase reversa em tempo real e convencional, seguidos de análise de sequência. Os dados clínicos foram obtidos a partir de registos médicos e diários dos sintomas dos doentes.

Resultados Foram detetados RV em 566 (19%) de 3016 adultos sintomáticos, 102 (4%) a partir das suas 2539 amostras de seguimento e 67 (4%) de 1677 controlos assintomáticos. A genotipagem foi bem sucedida em 538 (95%) indivíduos sintomáticos, 86 (84%) infeções de seguimento e 62 (93%) controlos. O RV-A foi a espécie predominante, associada a um risco acrescido de ITRI em comparação com o RV-B (risco relativo (RR), 4,5; 95% IC 2,5 a 7,9; $p < 0,001$) e RV-C (RR 2,2; 95% IC 1,2 a 3,9; $p = 0,010$). Em sujeitos sintomáticos, as cargas de RV-A foram superiores às de RV-B ($p = 0,015$). As pontuações dos sintomas e a duração foram semelhantes entre as espécies. Mais doentes infetados com RV-A sentiram um mau estar generalizado em comparação com RV-C ($p = 0,023$). Dos 140 tipos de RV identificados, cinco foram tipos novos, sendo que as infeções sintomáticas foram associadas a múltiplos tipos.

Interpretação Em adultos, o RV-A é significativamente detetado com maior frequência em casos com tosse aguda/ITRI do que o RV-C, enquanto a infeção por RV-B é frequentemente encontrada em doentes assintomáticos.

INTRODUCTION

Rhinoviruses (RVs) are the most prevalent respiratory pathogens in humans, accounting for approximately 20%–50% of respiratory tract infections (RTIs) annually.^{1–4} Infection with RV can lead to a wide spectrum of clinical manifestations ranging from asymptomatic to severe lower respiratory illness.^{2,5,6} RV is also recognised as a major cause of exacerbations of chronic obstructive pulmonary disease (COPD), asthma and cystic fibrosis.^{7,8} Coinfections with other viral or bacterial pathogens have been frequently reported, potentially increasing clinical severity.^{9,10} Over 160 RV types have been identified and classified into three genetically distinct species (RV-A, RV-B and RV-C) within the genus Enterovirus of the family Picornaviridae.¹¹ RV-A has been the most frequently detected RV species, followed by RV-C and RV-B, respectively.^{3,4} Although the clinical significance of RV species and types remains poorly defined, RV-C has been predominantly linked to asthma exacerbations

Key messages

What is the key question?

► What is the epidemiology and clinical impact of the different rhinovirus (RV) species.

What is the bottom line?

► RV-A was significantly more often detected in adults with acute lower respiratory tract infections than RV-C, while RV-B infection was often found in asymptomatic patients.

Why read on?

► The epidemiology and clinical impact of RVs is poorly understood and this is the most comprehensive assessment of RV species-specific clinical outcomes in adults with symptoms of lower respiratory tract infection visiting their general practitioner.

and more serious respiratory illness in young children.^{12–14} More recently similar clinical presentations across species have been reported.^{15–18}

Despite the high morbidity and disease burden of RV infections, there are currently no effective and safe antiviral treatments, and efforts to develop an effective vaccine have been hampered by the substantial antigenic diversity between RV types and species. A more practical approach could be the development of vaccines targeting more prevalent or pathogenic RV types although the feasibility of this depends on whether particular RV species or types are associated with more frequent or severe respiratory illness. Previous studies have been limited by the absence of asymptomatic controls and incomplete microbiological investigation, and were focused mainly on hospitalised young children.

The aim of this study was to determine the epidemiology and clinical impact of the different RV species through a, community-based comparative evaluation of disease severity among adult subjects infected with different RV species and types. Additionally, the multicentre approach provides insight in geographical differences in RV epidemiology.

METHODS

Study design and subjects

Respiratory samples were obtained from subjects aged 18 years and older enrolled as part of the genomics to combat resistance against antibiotics community-acquired lower respiratory tract infections (LRTIs) in Europe (GRACE) European Network of Excellence (www.grace-lrti.org) focusing on impro-



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ving the management of community-acquired LRTIs. Sixteen primary care networks from 11 European countries including: Belgium (Antwerp and Ghent); France (Nice), Germany (Rotenberg), Italy (Milan), the Netherlands (Utrecht), Poland (Bialystok, Lodz and Szczecin), Slovakia (Bratislava), Slovenia (Jesenice), Spain (Barcelona and Mataró), Sweden (Jönköping) and UK (Cardiff and Southampton) participated in prospective recruitment of patients presenting with acute cough and signs of an acute LRTI over the period October 2007–June 2010. Cases were patients presenting at the general practitioner (GP) with an acute or worsened cough (≤ 28 days duration) as the main symptom, or any clinical presentation considered by the GP to be caused by LRTI and consulting for the first time for this illness episode. Exclusion criteria were pregnancy, breast feeding and any condition associated with severe impaired immune status. Asymptomatic controls were subjects who consulted their GP for complaints other than respiratory, who had no symptoms and signs of a RTI and had not used antibiotics or antivirals in the previous 2 weeks. Case and controls were recruited from the same GP centre, within 14 days of each other and with a maximum 5-year age difference.

Nasopharyngeal swab (NPS) and sputum (if available) samples were collected from case (V1) and control (C1) patients during their first visit to the GP, for which standardisation was obtained by training of staff. Follow-up NPS samples were obtained from case patients at the second visit (V2) to the GP after approximately 28 days. Medical ethics committees in participating countries approved the study and all participants provided written informed consent.

The original study was designed to evaluate the aetiology of LRTIs in GP settings, as described by Ieven *et al*, this study is a post hoc analysis.¹⁹

Data collection

Clinical data, including medical history, comorbidities and their management/treatment, and days the patient felt unwell were recorded by the GP on a case report form (CRF) at the first consultation. The presence or absence of cough, sputum production, shortness of breath, wheeze, coryza, fever, chest pain, muscle aching, headache, disturbed sleep, feeling generally unwell, interference with normal activities, confusion/disorientation and diarrhoea, were documented. If present, the severity of each symptom was rated on a 4-point scale ranging from 'no problem=1' to 'severe problem=4'. Following the first GP consultation, patients were requested to complete a daily symptom diary for the duration of illness (to a maximum of 28 days). The presence and severity of the above symptoms (except diarrhoea) were rated on a 7-point scale ranging from 'normal/ not affected=0' to 'as bad as it could be=6'.

Clinical assessment

The disease severity of RV infections was evaluated by comparing the following clinical characteristics: (1) initial symptom score, (2) duration of illness, (3) maximal symptom score and (4) duration of higher symptom score. The 'initial symptom score' was estimated as the mean severity score of at least 12 of the 14 symptoms evaluated by the GP during the first visit of the patient. The 'duration of illness', 'maximal symptom score' and 'duration of higher symptom score' were estimated based on the presence and severity of 13 symptoms excluding diarrhoea, recorded in the patient's daily symptom diary as described previously. The duration of illness was defined as the total sum of days a patient felt unwell before the first GP visit and the number of days the patient experienced any of the 13 symptoms over the 28 days follow-up period. The duration of higher symptom score was the number of days a patient had a mean daily symptom score of two or more based on the 7-point scale.²⁰ The occurrence and severity of each symptom recorded during the first visit to the GP were also compared between RV species.

Laboratory investigation

The overall results of the laboratory diagnostics were previously described by Ieven *et al*.¹⁹ In short, total nucleic acids were extracted at the University Hospital Antwerp, and examined for RV by real-time PCR (RT-PCR) at the Leiden University Medical Center. Cycle quantifica-

tion (Cq) values, which had been normalised using a fixed baseline fluorescence threshold, were used as an indicative measure of viral load. Bacterial and fungal infections were detected in NPS or/and sputum samples by conventional culture and/or molecular methods.²¹

RV typing

RV genotyping was conducted by amplification and sequencing of partial VP3/VP1, VP4/VP2 or/and 5' - untranslated region (5'-UTR) viral genome fragments as described previously.²⁰ Basic local alignment search tool with nucleotide database (BLASTn) analyses were conducted for initial species identification and then confirmed by phylogenetic analysis. RV sequences were compared with prototype strains and assigned to types based on phylogenetic analysis and pairwise p distances (see online supplementary appendix). RV sequences from this study have been deposited in GenBank under the accession numbers KP736530-KP737279 and KR045604.

Statistical analysis

Continuous variables were summarised as medians with IQR ranges or means with 95% CI and for categorical variables, the frequencies in each category were calculated. Demographic and clinical characteristics were compared across RV species within RV-positive symptomatic and asymptomatic adults by using risk ratio and/or χ^2 tests for categorical variables and the non-parametric Kruskal-Wallis test, Mann-Whitney U test or independent t-test or one-way analysis of variance when appropriate for continuous variables. Correction for possible confounders (age, sex, geographical location, sample season and sample year) was performed using multivariable linear or logistic regression for continuous or binary outcome measures, respectively. The statistical analyses were conducted in the IBM SPSS Statistics software V.25 for Windows (IBM). A two sided $p < 0.05$ was considered statistically significant.

RESULTS

RV detection and species distribution

In this study, 3070 (99%) (median age 50, (IQR 36–63 years); male/female ratio 1:1.5) of 3104 recruited adults with acute cough/LRTI and 1677 asymptomatic controls (median age 50, (IQR 35–62 years); male/female ratio 1:1.5) were included. Thirty-four patients with no available NPS material or CRF were excluded (figure 1). NPS samples were obtained from 3016 symptomatic patients during the first visit (V1) to the GP and a follow-up (V2) sample was collected from 2485 (82%) of these patients.²⁰ For 54 symptomatic patients, only a follow-up NPS was available for testing, resulting in a total of 2539 V2 NPS specimens. Of the asymptomatic controls 1677 samples were tested. Of the 3104 symptomatic patients 1844 (60%) tested positive for a respiratory pathogen, of which 350 (11%) a bacterial pathogen only, 1190 (39%) a respiratory virus and 304 (10%) a double infection. Of the 1677 asymptomatic controls, 205 (12%) had an respiratory virus as previously reported by Ieven *et al*.¹⁹

RV was detected in 766 out of 7232 samples (11%) and genotyping was successful for 717 (94%) of these samples. Enteroviruses, including 13 EV-D68, 10EV-C104, 5EV-C105, 2EV-C117 types and 1EV-C (non-typeable), were identified due to cross-reactivity in our diagnostic RV assay. These 31 EV-positive samples were excluded from further analysis. Forty-nine (6%) RV-positive samples with lower viral loads inferred from quantification cycle (Cq) values could not be genotyped due to amplification failure in the genotyping PCR (median Cq values of 29 vs 36 in the diagnostic RT-PCR assay for genotyped and not-genotyped samples, respectively; $p < 0.001$).

RV was detected in 566 (19%) V1 and 102 (4%) V2 samples from case patients (of which 21 were positive in both the V1 and V2 samples) and in 67 (4%) C1 samples from asymptomatic control patients.²⁰ Of the 735 RV infection episodes, 182 (25%) were coinfections, of which 68 (9%) with another virus, 103 (14%) with a bacterial coinfection and 11 (2%) had an RV infection with at least two other pathogens. Commensals and *Candida species* were not considered causative pathogens and were excluded from the analysis.

Symptomatic (V1 positive) RV-positive patients tended to be older than asymptomatic patients (median 47 years, (IQR 33–60

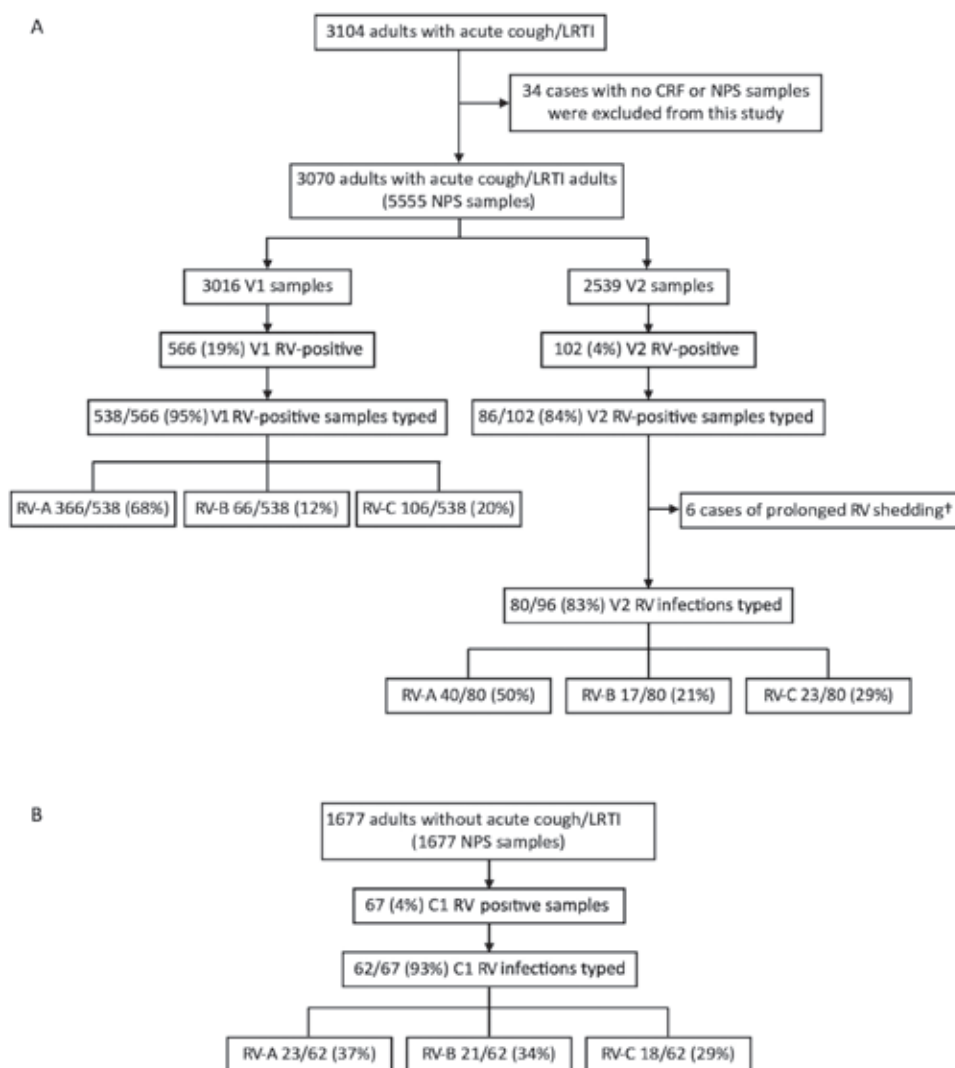


Figure 1 Rhinovirus prevalence and species distribution among (A) adults enrolled with acute cough/ LRTI and asymptomatic (B) controls. CRF, case report form; LRTI, lower respiratory tract infection; NPS, nasopharyngeal swab; RV, rhinovirus. †Prolonged rhinovirus shedding was identified in 6 patients.

years) vs median 38 years (IQR 27–58 years); $p=0.058$, respectively), see table 1. No significant differences were found in sex, location and sample season and year between RV-positive symptomatic and asymptomatic adults. Of 563 of the 566 V1 patients underlying conditions were stated: 238 (42%) had an underlying condition, including 122 (51%) with respiratory comorbidities or history of hospitalisation for respiratory illness. Mixed infections within the RV-positive adults (V1) were associated with symptomatic disease more often (29% vs 7% in the asymptomatic patients, RR 4.9 (95% CI 2.0 to 11.8) $p<0.001$, adjusted for age, sex, geographical location, sample season, sample year and viral load). Mixed infections were not included in further analyses. The RV-viral load was lower in the RV-positive asymptomatic controls (mean Cq value 31 vs 28 in patients, $p<0.001$, adjusted for age, sex, geographical location, sample season, sample year and mixed infections).

Virus genotyping to RV species level was successful in 538 (95%) V1, 86 (84%) V2 RV-positive samples from symptomatic patients and in 62 (93%) C1 control subjects. The number and proportion of RV species among symptomatic, follow-up and asymptomatic infections are shown in figure 1. Prolonged RV shedding in symptomatic patients (V1) was identified in six patients as previously described.²⁰ RV reinfection with another RV type was identified in 11 symptomatic (V1) patients.

Clinical manifestations

Complete clinical record forms and symptom diaries were available for 563 (99.5%) and 383 (67.7%) RV-positive symptomatic V1 patients, respectively. Age and sex characteristics of symptomatic and asymptomatic subjects, infection outcome, viral loads inferred

from Cq values and duration and severity of disease were compared across RV species (table 2). The age and sex distribution was similar across RV-species in the symptomatic

and control groups. In 538 RV-infected symptomatic patients the proportion of RV-A infections was 68% vs 12% for RV-B and 20% for RV-C infections. In contrast, in the 62 asymptomatic infections the proportions were similar: RV-A: 37%, RV-B: 34% and RV-C: 29% (figure 1). For single infections RV-A was 4.5 and 2.2 times more often associated with a LRTI outcome than

RV-B ($p<0.001$) and RV-C ($p=0.010$), respectively, and RV-C more often than RV-B (RR 2.1, $p=0.015$). The results were similar for RV coinfecting cases. In symptomatic patients with a RV monoinfection RV-A viral loads (mean Cq=27) were significantly higher than RV-B viral loads (mean Cq=30, $p=0.015$). The duration, overall disease severity, and maximum daily symptom score were similar between RV species. The severity of the individual symptoms was also compared across RV species (table 3). Significant differences were observed only for ‘feeling generally unwell’. In particular RV-A infected patients generally felt worse than those with RV-C ($p=0.023$). No other significant differences were observed between RV-A and RV-B, or RV-C and RV-B infected patients.

RV prevalence and species distribution according to site and year of detection

The number of tested NPS samples, RV detection rate and species distribution among the 16 sites in Europe over the 3 years study period are presented in figure 2. The majority of subjects were recruited in the months October to April and years were defined from July until June of the following year. No patients were recruited

Table 1 Demographics of symptomatic (V1) vs asymptomatic (C1) RV-positive patients

	Total n=633	RV +V1 n=566	RV +C1 n=67	P value
Male (%)	263 (42)	229 (40)	34 (51)	0.106
Age (median, IQR)	47 (32–60)	47 (33–60)	38 (27–58)	0.058
Ethical background (%)	563			
Caucasian		540 (96)		
African		8 (1)		
Asian		10 (2)		
Other		5 (1)		
Study site (%)				0.281
Antwerp BE	95 (15)	85 (15)	10 (15)	
Barcelona SP	66 (10)	64 (11)	2 (3)	
Bialystok PL	28 (4)	24 (4)	4 (6)	
Bratislava SL	30 (5)	29 (5)	1 (1)	
Cardiff GB	64 (10)	57 (10)	7 (10)	
Ghent BE	25 (4)	20 (4)	5 (7)	
Jesenice SVN	10 (2)	10 (2)	0 (0)	
Jonkoping SW	8 (1)	7 (1)	1 (1)	
Lodz PL	52 (8)	47 (8)	5 (7)	
Mataró SP	79 (12)	68 (12)	11 (16)	
Milan IT	7 (3)	17 (3)	0 (0)	
Nice FR	3 (0.5)	3 (1)	0 (0)	
Rotenberg DU	27 (4)	25 (4)	2 (3)	
Southampton GB	43 (7)	39 (7)	4 (6)	
Szczecin PL	27 (4)	22 (4)	5 (7)	
Utrecht NL	59 (9)	49 (9)	10 (15)	
Sample season and year (%)	632	565	67	0.918*
Autumn 07	37 (6)	34 (6)	3 (4)	
Winter 07/08	49 (8)	43 (8)	6 (9)	
Spring 08	73 (12)	67 (12)	6 (9)	
Summer 08	4 (1)	4 (1)	0 (0)	
Autumn 08	118 (19)	106 (19)	12 (18)	
Winter 08/09	64 (10)	55 (10)	9 (13)	
Spring 09	44 (7)	40 (7)	4 (6)	
Summer 09	4 (1)	4 (1)	0 (0)	
Autumn 09	131 (37)	118 (21)	13 (19)	
Winter 09/10	77 (12)	69 (12)	8 (12)	
Spring 10	31 (5)	25 (4)	6 (9)	
Underlying condition (%)		238/563 (42)		
Asthma		67/563 (12)		
COPD		41/563 (7)		
Other respiratory comorbidities		7/563 (1)		
History of hospitalisation for respiratory illness		24/563 (4)		
Cardiac disease		47/563 (8)		
Diabetes		35/562 (6)		
Allergic diseases		105/563 (23)		

*Overall sample season and year, symptomatic (V1) vs asymptomatic (C1).
COPD, chronic obstructive pulmonary disease; RV, rhinovirus.

ted from Nice, Bialystok, Szczecin, Bratislava and Jesenice during 2007/2008 and only 9 samples from six patients were available from Milan for 2009/2010. RV accounted for 1% up to 21% of respiratory infections per site during a particular year, when excluding Milan during 2009/2010, because of the low number of included cases.

RV type identification

Of the 686 sequenced RVs, 654 (95%) were characterised by partial VP3/VP1 or/and VP4/VP2 sequencing and 32 (5%) based only on the 5'-UTR (see online supplementary appendix). The latter were assigned only to species taxa level, because of limited phylogenetic discrimination in the 5'-UTR region. Four VP4/VP2 sequences were classified only to species level based on BLASTn results due to poor sequence quality. A total of 650 RV sequences were assigned to 73 RV-A, 25 RV-B and 42 RV-C types representing 91%, 78% and 76%, 11 respectively, of the currently established types within each species (figure 3). Five new RV types were identified and assigned by the Picornaviridae study group as RV-A type A109, RV-B types B105 and B106 and RV-C types C52 and C53.

DISCUSSION

In our study, RV was detected in 19% of adults with acute cough/LRTI and in 4% of follow-up samples as well as samples from asymptomatic controls. The overall annual prevalence ranged from 1% to 21% between and within communities. These data indicate that the burden of RV associated illness varies substantially within and between communities in different years. Several other studies have reported rates of RV infection from 7% to 33% in inpatient and outpatient adults with acute LRTI or influenza-like illness,^{15 22–25} and in 8% or less of asymptomatic adults.^{3 4 15 26}

RV species were identified with a different frequency among symptomatic and control subjects. With 68% prevalence RV-A strains were significantly more common in RV infected symptomatic patients than RV-B (12%) or RV-C (20%) strains. In contrast, the prevalence of RV-A (37%), RV-B (34%) and RV-C (29%) was more or less similar in asymptomatic infections, suggesting a more pathogenic role of RV-A infections. Also, RV-A was 4.5 and 2.2 times more often associated with LRTI than RV-B and RV-C ($p<0.010$), and RV-C 2.1 times more often than RV-B ($p=0.015$).

Our findings indicate that in adults, the prevalence of RV-associated LRTI is considerably higher than that of RV-B and RV-C, while RV-B infections are more often asymptomatic. The latter observation is further supported by the fact that RV-B has been detected infrequently in children and adults hospitalised for severe respiratory illness.^{15 17 27–31} Furthermore RV-B symptomatic infections had significantly lower viral loads than RV-A symptomatic infections, suggesting lower pathogenicity of RV-B viruses. Lower viral loads of RV-B relative to RV-A and RV-C in respiratory specimens have previously been reported for adults with pneumonia³² and viral load has been reported as indicator for severity of RV infections.³ These findings are in agreement with the *in vitro* study that demonstrated that RV-B types replicate less efficiently and induce lower cytokines and/or chemokine levels than RV-A or RV-C infections.³³

Our results on RV species distribution (RV-A>RV-C>RV-B) among adults with LRTI are consistent with those from a study conducted in Seoul among adults with pneumonia.³² Other studies in symptomatic patients found a lower prevalence of RV-C than RV-B infections.^{34 35} These differences in the relative proportions of RV species in comparison to our findings could be due to differences in the study populations (eg, upper respiratory tract infection (URTI) instead of LRTI) and annual variations in species distribution. We observed no significant differences between RV species in the duration of illness, maximum symptom scores, overall disease severity and severity of individual common cold symptoms. However, RV-A infected patients subjectively felt in general worse than those infected with RV-C. Our results suggest that RV-A infections have a more debilitating impact on the general health as compared with RV-B and RV-C infections. In children several studies demonstrated an association between RV-C and more serious respiratory illness.^{13 22,28}

In adult patients RV-C infection has been reported to cause more frequent acute RTI and appeared more severe as compared with children.^{22 36} Other studies in adults observed no differences in disease severity between RV species,^{15 16 26 32 37} though one study found a higher disease severity associated with RV-A in upper respiratory symptoms.³⁵ However, these studies are limited due to the short surveillance periods, lack of asymptomatic controls and small sample size. It must be noted that the patients included in this study had per definition acute cough/LRTI, thus differences in disease severity between RV species in patients with milder symptoms cannot be excluded. RV-A was the most prevalent species in the majority of study locations, followed by RV-C, while RV-B occurrence varied considerably between and within certain communities. Substantial antigenic variation within RV-A could lead to more frequent reinfections in the community and to a higher overall prevalence.

Interestingly, not all RV species were identified in the separate locations during the study period. Genotyping of the RV samples lead to the discovery of 5 novel RV types and revealed a remarkably high diversity of RVs represented by 73 RV-A, 25 RV-B and 42 RV-C types. Asymptomatic infections were associated with a variety of RV types, the majority of which were also identified in symptomatic cases.

Table 2 Age and sex distribution, infection outcome and disease severity according to rhinovirus species

Characteristics*	RV-A	RV-B	RV-C	RR (95%CI)	P value
Age/sex -V1 infections					
No of cases	366	66	106		
Median (IQR) years	47 (33–60)	43 (30–61)	50 (33–62)		0.571
No (%) of male	155 (42)	22 (33)	43 (41)		0.389
Age/sex -C1 infections					
No of cases	23	21	18		
Median (IQR) years	37 (25–53)	36 (28–51)	50 (30–61)		0.472
No (%) of male	13 (57)	9 (43)	10 (56)		0.613
Symptomatic (V1) vs asymptomatic (C1) infections	366 (94)/23 (6)	66 (76)/21 (24)	106 (85)/18 (15)	RV-A vs RV-B: RR 4.6 (2.7 to 8.0)	RV-A vs RV-B (<0.001)†
No (%) of V1/C1 cases				RV-A vs RV-C: RR 2.4 (1.4 to 4.3)	RV-A vs RV-C (0.003)†
				RV-C vs RV-B: RR 1.9 (1.1 to 3.4)	RV-C vs RV-B (0.026)†
Symptomatic (V1) vs asymptomatic (C1) single infections	261 (92)/22 (8)	43 (70)/18 (32)	80 (82)/17 (18)	RV-A vs RV-B: RR 4.5 (2.5 to 7.9)	RV-A vs RV-B (<0.001)†
No (%) of V1/C1 cases				RV-A vs RV-C: RR 2.2 (1.2 to 3.9)	RV-A vs RV-C (0.010)†
				RV-C vs RV-B: RR 2.1 (1.1 to 3.7)	RV-C vs RV-B (0.015)†
Cq values- V1 single infections	27 (27 to 28)	30 (28 to 31)	27 (26 to 29)		0.053 RV-A vs RV-B (0.015)†
Mean (95% CI)					RV-A vs RV-C (0.780)†
					RV-C vs RV-B (0.068)†
Cq values- C1 single infections	31 (29 to 33)	32 (30 to 33)	31 (29 to 32)		0.838† RV-A vs RV-B (0.922)†
Mean (95% CI)					RV-A vs RV-C (0.576)†
					RV-C vs RV-B (0.642)†
Initial symptom score‡					0.697† RV-A vs RV-B (0.426)†
No of cases	260	43	80		RV-A vs RV-C (0.666)†
Median (IQR)	1.6 (1.1–2.0)	1.4 (0.9–2.1)	1.4 (1.1–1.9)		RV-C vs RV-B (0.684)†
Duration of illness					0.987† RV-A vs RV-B (0.893)†
No of cases	200	31	62		RV-A vs RV-C (0.948)†
Median (IQR) days	21 (14–31)	20 (13–31)	19 (13–32)		RV-C vs RV-B (0.870)†
Maximal daily symptom score§					0.426† RV-A vs RV-B (0.216)†
No of cases	200	31	62		RV-A vs RV-C (0.519)†
Median (IQR)	2.3 (1.6–3.1)	2.0 (1.3–3.1)	2.2 (1.5–3.0)		RV-C vs RV-B (0.499)†
Duration of higher symptom score					0.942† RV-A vs RV-B (0.985)†
No of cases	158	23	48		RV-A vs RV-C (0.740)†
Median (IQR) days	4 (3–7)	4 (2–7)	3 (2–6)		RV-C vs RV-B (0.842)†

*Characteristics related to disease severity and duration of illness were evaluated only for patients with rhinovirus single infections who had complete case report forms or/and symptom diaries.

†Corrected for age, sex, sample season and sample year.

‡Initial symptom score scale: 1=no problem, 2=mild problem, 3=moderate problem, 4=severe problem.

§Maximal daily symptom score scale: 0=no problem/not affected, 1=very little problem, 2=slight problem, 3=moderately bad, 4=bad, 5=very bad, 6=as bad as it could be.

Cq, cycle of quantification; RR, relative risk; RV, rhinovirus

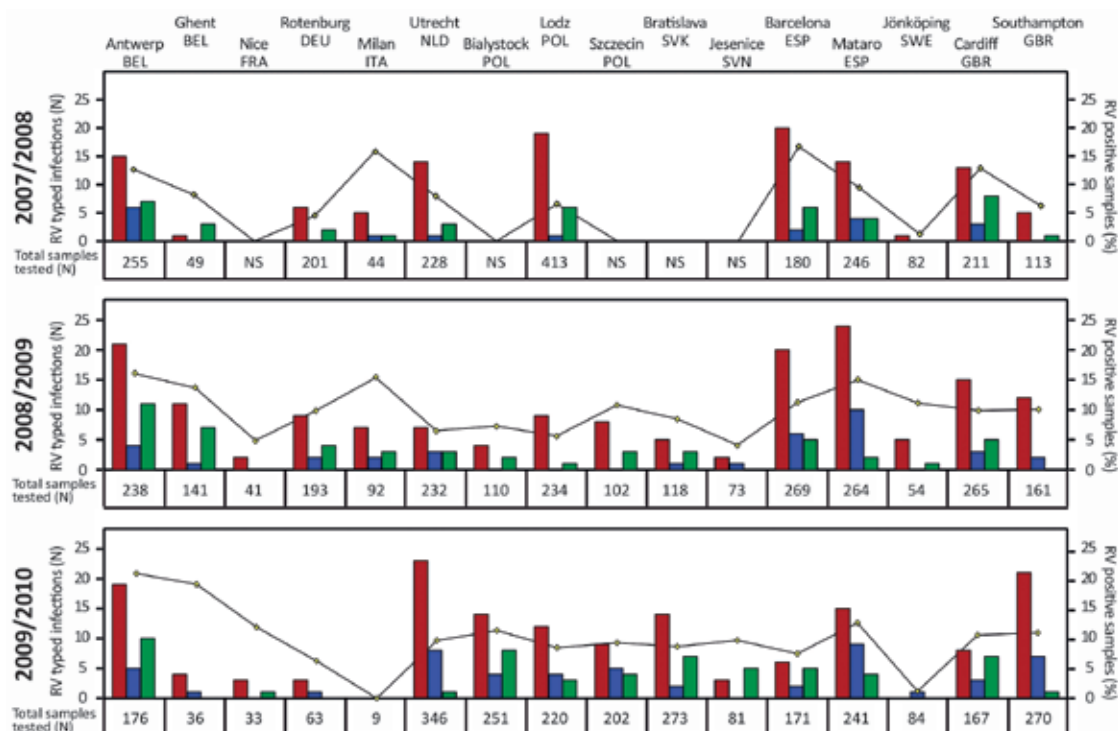


Figure 2 Rhinovirus (RV) detection rate and species distribution according to site and year of detection. Total numbers of tested samples per location and year of isolation are presented under the corresponding country panel; 'NS' designates that no samples were available. Plot lines represent the proportion (%) of RV infections (right side y-axis) and bar graphs represent the number of RV-A (red), RV-B (blue) and RV-C (green) infections (left side y-axis). Country abbreviations: BEL (Belgium), FRA (France), DEU (Germany), ITA (Italy), NLD (Netherlands), POL (Poland), SVK (Slovakia), SVN (Slovenia), ESP (Spain), SWE (Sweden), GBR (United Kingdom).

Table 3 Frequency and severity of symptoms in adults with rhinovirus associated acute cough/LRTI

Characteristics	No (%) of events (absent-mild/moderate-severe)*			P value†
	RV-A n=261	RV-B n=43	RV-C n=80	
Cough	1 (0.4)/260 (99.6)	1 (2)/42 (98)	1 (1)/79 (99)	RV-A vs RV-B (0.053) RV-A vs RV-C (0.400) RV-B vs RV-C (0.180)
Phlegm	131 (50)/130 (50)	22 (51)/21 (49)	48 (60)/32 (40)	RV-A vs RV-B (0.739) RV-A vs RV-C (0.091) RV-B vs RV-C (0.397)
Shortness of breath	171 (66)/90 (34)	27 (63)/16 (37)	55 (69)/25 (31)	RV-A vs RV-B (0.549) RV-A vs RV-C (0.578) RV-B vs RV-C (0.371)
Wheeze	199 (76)/62 (24)	32 (74)/11 (26)	64 (80)/16 (20)	RV-A vs RV-B (0.798) RV-A vs RV-C (0.606) RV-B vs RV-C (0.566)
Running nose	109 (42)/152 (58)	21 (49)/22 (51)	37 (46)/43 (54)	RV-A vs RV-B (0.306) RV-A vs RV-C (0.667) RV-B vs RV-C (0.545)
Fever	226 (87)/35 (13)	38 (88)/5 (12)	69 (86)/11 (14)	RV-A vs RV-B (0.958) RV-A vs RV-C (0.883) RV-B vs RV-C (0.962)
Chest pain	205 (79)/56 (21)	32 (74)/11 (26)	60 (75)/20 (25)	RV-A vs RV-B (0.352) RV-A vs RV-C (0.534) RV-B vs RV-C (0.690)
Muscle aching	189 (72)/72 (28)	32 (74)/11 (26)	58 (73)/22 (27)	RV-A vs RV-B (0.662) RV-A vs RV-C (0.990) RV-B vs RV-C (0.708)
Headache	181 (69)/80 (31)	25 (58)/18 (42)	55 (69)/25 (31)	RV-A vs RV-B (0.287) RV-A vs RV-C (0.996) RV-B vs RV-C (0.361)
Disturbed sleep	141 (54)/120 (46)	25 (58)/18 (42)	38 (48)/42 (52)	RV-A vs RV-B (0.428) RV-A vs RV-C (0.259) RV-B vs RV-C (0.150)
Diarrhoea	256 (98)/5 (2)	41 (95)/2 (5)	78 (98)/2 (2)	RV-A vs RV-B (0.087) RV-A vs RV-C (0.744) RV-B vs RV-C (0.225)
Confusion/ disorientation	257 (98)/4 (2)	43 (100)/0	79 (99)/1 (1)	RV-A vs RV-B (0.999) RV-A vs RV-C (0.999) RV-B vs RV-C (0.999)
Interference with normal activities	156 (60)/105 (40)	23(53)/20 (47)	54 (68)/26 (33)	RV-A vs RV-B (0.364) RV-A vs RV-C (0.281) RV-B vs RV-C (0.130)
Feeling generally unwell	118 (45)/143 (55)	22 (51)/21(49)	49 (61)/31 (39)	RV-A vs RV-B (0.442) RV-A vs RV-C (0.023) RV-B vs RV-C (0.392)

* The presence and severity of symptoms were evaluated only for patients with rhinovirus single infections.

† Corrected for age, sex, sample season and sample year.

LRTI, lower respiratory tract infection; RV, rhinovirus.

Although comprehensive, this study has some limitations. Due to the heterogeneity of the RV genomes, our RV diagnostic and genotyping assays might have varied in efficacy of amplification, and therefore, be suboptimal for some genotypes. In particular, RV-C infections might be somewhat underrepresented, since a limited number of RV-C complete genome sequences were available at the time our diagnostic assay was developed. In addition, due to the nature of this study, only associations can be found, and no causality can be proven. With the current study design, an association can be made between RV type and disease severity. However, the population studied, is patients visiting their GP that in general will be older and have more comorbidities as compared with the general population. Nevertheless, these are the patients consulting their GP, and therefore, this study is very representative for clinical practice.

Although limited, some CRF's were missing and not all RV positive samples could be typed. Because these numbers are limited a link between the missing data and disease severity is not expected and this probably will not result in a bias. Finally, the clinical status of cases with RV-positive follow-up samples could not be clearly defined, since symptom manifestations were not recorded by the GP at the time of the second visit.

This is a very comprehensive study, in which RV typing has been performed in symptomatic (LRTI) and asymptomatic adult

GP patients in 11 countries. RV typing is not part of standard diagnostic care and our results do not provide an indication for an added value in relation to disease severity. This may change in the future if subtype differences in efficacy are observed following antiviral treatment or vaccination.

In conclusion, LRTI in adults were mainly associated with RV-A, identified in a significantly higher proportion of symptomatic than asymptomatic subjects as compared with RV-B and RV-C. Furthermore RV-A symptomatic infections were associated with significantly higher viral loads than RV-B symptomatic infections, suggesting lower pathogenicity of RV-B.

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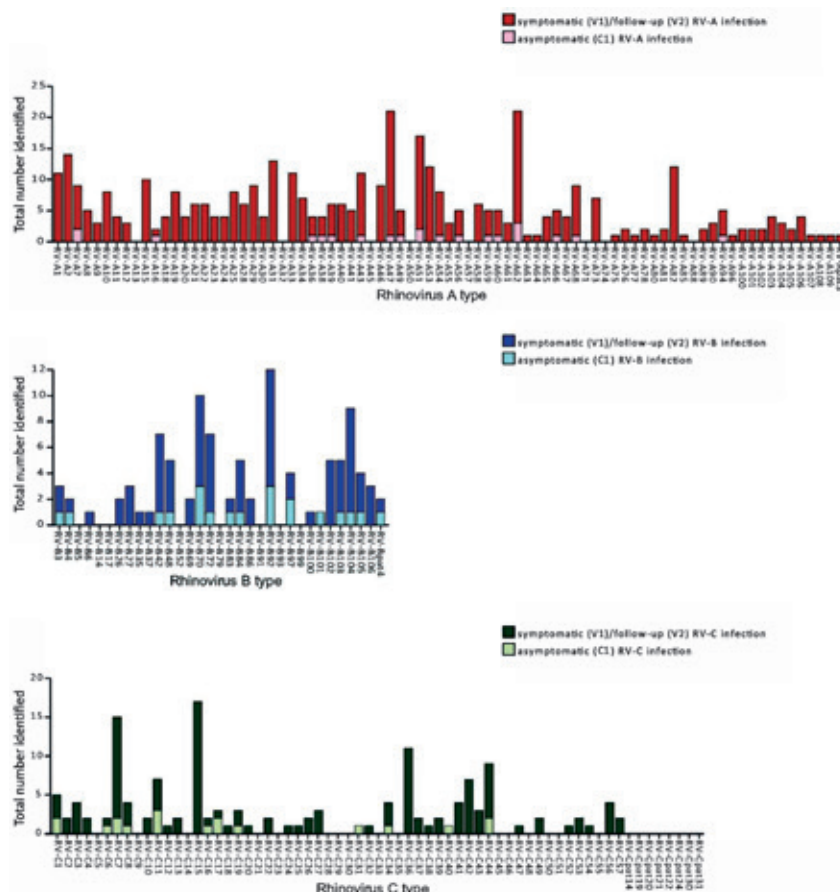


Figure 3 Frequencies of rhinovirus types identified in symptomatic case and asymptomatic control adults.

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Data availability statement Data are available on reasonable request. RV sequences from this study have been deposited in GenBank under the accession numbers KP736530-KP737279 and KR045604.

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ARTIGO ORIGINAL INVESTIGAÇÃO

Carga viral no tracto respiratório superior em indivíduos assintomáticos e doentes ligeiramente sintomáticos com infeção por SARS-CoV-2

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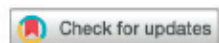
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RESUMO

Contexto Indivíduos assintomáticos com infeção por SARS-CoV-2 possuem cargas virais viáveis e têm sido associados a vários casos de transmissão. No entanto, faltam dados sobre as cargas virais nestes indivíduos. Avaliámos as cargas virais em indivíduos assintomáticos com infeção por SARS-CoV-2 em comparação com as de doentes sintomáticos com COVID-19.

Métodos Os participantes do estudo foram recrutados numa instalação comunitária concebida para o isolamento de doentes com COVID-19 ligeira na Coreia do Sul. A presença de sintomas foi avaliada por meio de um inquérito baseado em questionário. As cargas virais no trato respiratório superior foram medidas por transcrição reversa em tempo real - PCR (RT-PCR) visando os genes E, RdRp e N do SARS-CoV-2, com um valor de limiar de ciclo (Ct) de 40 para determinar a positividade.

Resultados Em 213 doentes com infeção por SARS-CoV-2, 41 (19%) permaneceram assintomáticos devido potencial exposição através de confirmação laboratorial e admissão; destes, 39 (95%) foram submetidos a testes RT-PCR de seguimento após uma mediana de 13 dias. Em 172 doentes sintomáticos, 144 (84%) foram submetidos a testes RT-PCR de seguimento. Vinte e um (54%) indivíduos assintomáticos e 92 (64%) doentes sintomáticos testaram positivo para SARS-CoV-2 durante o seguimento. Indivíduos assintomáticos e doentes sintomáticos não apresentaram quaisquer diferenças significativas nos valores Ct médios dos genes E (31,15 vs 31,43; $p>0,99$), RdRp (32,26 vs 32,93; $p=0,92$) e N (33,05 vs 33,28; $p>0,99$).

Conclusão Aproximadamente um quinto dos indivíduos sem sintomas graves encontravam-se assintomáticos e as suas cargas virais foram comparáveis às dos doentes sintomáticos. Uma grande proporção de doentes com sintomas ligeiros de COVID-19 ou de indivíduos assintomáticos com SARS-CoV-2 apresentaram resultados positivos persistentes de RT-PCR no seguimento.

INTRODUCTION

The presence of asymptomatic individuals with positive reverse transcription-PCR (RT-PCR) results for SARS-CoV-2 has been noted even in the early reports of the COVID-19 outbreak.^{1,2} Moreover, several case reports have suggested that the transmission of SARS-CoV-2 from asymptomatic individuals is possible.^{1–3} However, owing to the rapid spread of COVID-19 and the resulting shortage in PCR testing capabilities, asymptomatic individuals with SARS-CoV-2 infection are likely to go unnoticed by healthcare workers. Therefore, asymptomatic individuals have not been systematically evaluated in terms of their viral load and infectivity, and thus, the extent of their possible contribution to the community spread of COVID-19 is unknown.

In South Korea, a large cluster of COVID-19 cases was identified in Daegu City; this cluster was soon revealed to be related to a single religious group.⁴ Thereafter, Korean epidemiologic

Key messages

What is the key question?

► Do asymptomatic individuals with SARS-CoV-2 infection have the potential to significantly contribute to the community spread of COVID-19?

What is the bottom line?

► In a series of 213 patients with COVID-19 without severe symptoms, 19% were asymptomatic from potential exposure to laboratory confirmation and admission. Asymptomatic individuals had comparable loads of SARS-CoV-2 genes to symptomatic patients.

Why read on?

► Asymptomatic individuals were frequent among those infected with SARS-CoV-2, but harboured a comparable viral load compared with that of symptomatic patients and may thus act as a meaningful driving force for the community spread of COVID-19.

teams thoroughly traced the close contacts of this religious group and discovered more than 3000 cases of COVID-19 with a wide range of symptom severity, from none to severe. Those without severe symptoms were admitted to dedicated care facilities for isolation and monitoring. As a result of this unique situation, we were able to assess many asymptomatic individuals who were otherwise unlikely to be identified as cases of COVID-19.

Here, we assessed the viral load in the upper respiratory tract of asymptomatic individuals infected with SARS-CoV-2 using the cycle threshold (Ct) values of RT-PCR targeting SARS-CoV-2 genes and compared the results with those from patients with mild symptoms of COVID-19.

METHODS

Study participants

We recruited study participants from a community care facility designated for patients with COVID-19 without severe symptoms. The admission criteria were as follows: COVID-19 national early warning score <4; without high-risk profiles such as age ≥65 years, chronic illness, current smoker and those requiring supplemental oxygen due to low oxygen saturation <90%. This facility is located approximately 50 miles from Daegu City and housed a total of 260 patients at the time of this study.

In March 2020, we conducted a survey on the patients to gather information on any COVID-19 symptom as well as age, sex and underlying disease. Asymptomatic individuals were defined as those who did not report any of the following symptoms: fever ($>37.5^{\circ}\text{C}$), chills, myalgia, fatigue, rhinorrhea, nasal congestion, hyposmia, hypogeusia, sore throat, dyspnoea, cough, sputum production, haemoptysis, headache, dizziness, anorexia, nausea, vomiting, abdominal pain and diarrhoea. Patients participated in this study by filling out the survey, and written informed consent was obtained from each patient. Missing data were obtained with telephone interviews by trained physicians. This study was approved by the institutional review board of Asan Medical Center.

Sample acquisition

All sample acquisitions for follow-up RT-PCR at the care centre were carried out by experienced physicians donning the complete personal protective equipment. According to the Center for Disease Control guidelines⁵ for obtaining clinical specimens for confirming COVID-19, we obtained swab samples from both the nasopharynx and oropharynx and combined them in a single tube to maximise the sensitivity of the RT-PCR test and minimise the use of resources. The nasopharyngeal samples were obtained according to a previously reported method,⁶ in which swabs were inserted through the nostril to a distance equivalent to the outer opening of the ear canal and gently rubbed for several seconds to absorb the secretions. For oropharyngeal samples, the tonsillar pillars were swabbed. The nasopharynx and oropharynx were swabbed once each with separate swabs, placed in a single tube containing 300 μL of viral transport medium and transported to a reference laboratory under cold conditions for subsequent RNA extraction and RT-PCR testing.

RT-PCR for SARS-CoV-2 genes

Viral RNA from the upper respiratory tract swab samples was extracted using the MagNA Pure 96 System (Roche Diagnostics, Mannheim, Germany), according to the manufacturer's instructions. The resulting samples were tested for the E, RdRp and N genes of SARS-CoV-2 with real-time RT-PCR using the Allplex 2019-nCoV Assay kit (Seegene)⁷ with CFX96 Real-Time PCR Detection System (Bio-Rad, Hercules, California, USA) under the following condition: 20 min at 50°C for reverse transcription and 15 min at 95°C for denaturation as the initial step, followed by 45 cycles of 15 s each at 94°C and 30 s at 58°C . A Ct value of <40 was used as the cut-off for determining positivity, according to the manufacturer's instructions.

Statistical analysis

Categorical variables were compared using the Fisher's exact test or χ^2 test as appropriate, and continuous variables were compared using the Mann-Whitney U test or Student's t-test as appropriate. All tests of significance were two-tailed, and p values <0.05 were considered statistically significant. Continuous variables are represented as median values with IQR for non-normally distributed variables and as mean $\pm$ SD values for normally distributed variables. All statistical analyses were carried out in IBM SPSS Statistics for Windows, V.23.0 (IBM Corp., Armonk, New York, USA).

RESULTS

Of the 260 patients with COVID-19, 213 (82%) participated in this study. During the observation period, 41 (19%; 95% CI 15% to 25%) individuals remained asymptomatic, of whom 39 (95%) underwent follow-up RT-PCR testing at the care facility. Of the 172 (81%; 95% CI 75% to 86%) patients with mild symptoms of COVID-19, 144 (94%) underwent follow-up RT-PCR testing. Thus, a total of 183 patients (asymptomatic, $n=39$; symptomatic, $n=144$) with follow-up RT-PCR results were included in the analysis.

The baseline clinical characteristics of asymptomatic individuals and symptomatic patients are shown in table 1. On follow-up RT-PCR testing, 21 (54%) asymptomatic individuals and 92 (64%) symptomatic patients tested positive for SARS-CoV-2 genes

Table 1 Characteristics of asymptomatic individuals with SARSCoV-2 infection and symptomatic patients with COVID-19*

	Asymptomatic individuals (n=39)	Symptomatic patients (n=144)	P value
Age, median (IQR), y	25.0 (21.5–34.0)	26.5 (22.0–46.0)	0.22
Male sex, n (%)	22 (56)	62 (43)	0.14
Underlying diseases, n (%)	3 (8)	26 (18)	0.12
Hypertension	0	5	
Asthma	0	4	
Liver disease	0	2	
COPD	0	1	
Solid cancer	0	1	
Rheumatologic disease	1	0	
Other	2†	13‡	
Interval from the first swab for diagnosis to the start of isolation, median (IQR), days	6.0 (4.5–7.0)	6.0 (4.0–9.0)	0.84
Interval from initial confirmation to follow-up RT-PCR testing, median (IQR), days	12 (9–14)	13 (11–15)	0.06
Interval from symptom onset to follow-up RT-PCR testing, median (IQR), days	NA	26 $\pm$ 6	NA
Positive result on follow-up RTPCR testing, n (%)	21 (54)	92 (64)	0.25
Ct values, mean $\pm$ SD			
E gene	31.15 $\pm$ 2.72	31.43 $\pm$ 2.80	>0.99
RdRp gene	32.26 $\pm$ 2.86	32.93 $\pm$ 2.87	0.92
N gene	33.05 $\pm$ 2.52	33.28 $\pm$ 2.48	>0.99

*Categorical variables were compared using the Fisher's exact test or χ^2 test, as appropriate, and continuous variables were compared using the Mann-Whitney U test or Student's t-test.

All tests of significance were two-tailed.

†Includes thyroid disease ($n=1$) and allergic rhinitis ($n=1$).

‡Includes allergic rhinitis ($n=8$), hyperlipidaemia ($n=2$), thyroid disease ($n=2$) and nephrotic syndrome ($n=1$).
Ct, cycle threshold; NA, not available; RT-PCR, reverse transcription-PCR

($p=0.25$). The mean Ct values of the SARS-CoV-2 genes in asymptomatic individuals and symptomatic patients were as follows: E gene, 31.15 versus 31.43 ($p>0.99$); RdRp gene, 32.26 versus 32.93 ($p=0.92$) and N gene, 33.05 versus 33.28 ($p>0.99$) (table 1).

DISCUSSION

A recent study on 72 314 Chinese patients reported that the proportion of asymptomatic individuals with SARS-CoV-2 was approximately 1%.⁸ However, this study was based on patients from the Hubei Province, where the sudden shortage of healthcare resources is presumed to have led to a selection bias towards the exclusion of asymptomatic individuals and patients with mild symptoms. Therefore, the actual prevalence of asymptomatic cases of COVID-19 is most likely higher than 1%. Accordingly, we found that 19% of patients with COVID-19 had remained asymptomatic from potential exposure to laboratory confirmation and facility admission.

In our study, 54% of asymptomatic individuals and 64% of patients with mild symptoms showed positive results in the follow-up PCR testing conducted at a median of 13 days from diagnosis. Similarly, Xiao *et al* reported that in 301 patients with mild-to-moderate symptoms of COVID-19, the median duration from symptom onset to an effective negative SARS-CoV-2 result was 20 days.⁹ A recent Chinese study also reported that the median duration of viral shedding assessed by SARS-CoV-2 RT-PCR was 21 days in patients with mild COVID-19.¹⁰ These results suggest that patients with COVID-19 may experience a more protracted course than that initially hypothesised. However, our results should be interpreted with caution because positive RT-PCR results do not necessarily indicate the presence of viable virus, for which cell culture is needed for confirmation. Indeed, recent studies have shown that viable virus was isolated within 10 days from the symptom onset.^{11 12} Therefore, further studies are needed to determine whether the prolonged duration of positive RT-PCR results in asymptomatic individuals with SARS-CoV-2 infection or mildly symptomatic patients with COVID-19 can be translated into a continuous need for precaution and quarantine.

Previous studies have shown that viable SARS-CoV-2 was isolated from asymptomatic individuals and that a certain number of cases are likely to have been transmitted from asymptomatic individuals.^{12–15} Indeed, we found that asymptomatic individuals had RT-PCR Ct values for SARS-CoV-2 genes comparable with those of patients with mild symptoms of COVID-19. Considering that most asymptomatic individuals with COVID-19 are likely to go unnoticed by healthcare workers and continue to reside within communities, such individuals may act as an essential driving force for the community spread of COVID-19 and the ongoing pandemic state. Our data thus support the general public use of face masks as well as broadening the scope of SARS-CoV-2 testing to include asymptomatic persons in certain high-risk settings until such time as further data become available regarding the duration and transmissibility of viable virus shedding from asymptomatic individuals with SARS-CoV-2 infection to support these recommendations.

This study is limited in that the study population largely comprised those in their 20s and 30s, a characteristic that is likely linked to the demographic of the Shincheonji religious group. Therefore, the prevalence of asymptomatic individuals and their viral load may be different in other age groups. Moreover, there is a possibility of recall bias concerning the self-reports of symptoms; nevertheless, as the study participants were highly cooperative and well educated on the gravity of the current pandemic, we believe that such bias is not likely to have significantly affected our main results. Additionally, we could not obtain the results of the initial RT-PCR tests of the patients because each of them underwent RT-PCR tests at separate triages. Finally, the duration from the initial confirmation to follow-up RT-PCR testing for symptomatic patients was slightly longer than that for asymptomatic individuals; such a discrepancy occurred because the guideline of the community care facility recommended conducting follow-up RT-PCRs for patients after symptom resolution and at least 7 days after diagnosis. However, this bias is not likely to have substantially affected our main findings on the Ct values in the follow-up RT-PCR testing.

In conclusion, we report that as many as one-fifth of individuals with SARS-CoV-2 infection without severe symptoms were asymptomatic and the viral load in their nasopharynx was comparable to that in patients with mild symptoms. In addition, a large proportion

of mildly symptomatic patients or asymptomatic individuals showed persistent positive upper respiratory RT-PCR results at follow-up. Asymptomatic individuals with SARS-CoV-2 infection may contribute to the ongoing community spread of COVID-19, but further studies with cell culture are needed to evaluate the transmissibility of COVID-19 from asymptomatic individuals to inform a recommendation on universal personal protective equipment.

Author affiliations

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ARTIGO ORIGINAL INVESTIGAÇÃO

Limites de reprodutibilidade pediátrica para o volume expiratório forçado em 1 segundo

Sanja Stanojevic,^{1,2} Nicole Filipow,¹ Felix Ratjen^{1,3}

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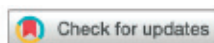
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RESUMO

Contexto Os padrões atuais de reprodutibilidade de espirometria foram derivados utilizando um pequeno conjunto de dados de adultos e poderão não ser ideais para a interpretação de medições repetidas da função pulmonar infantil.

Objetivo Definir limites de reprodutibilidade para a variação do volume expiratório forçado em 1 segundo (FEV₁) que representem a variabilidade normal de um indivíduo entre consultas em crianças saudáveis e avaliar estes limites como uma ferramenta para monitorizar crianças com fibrose quística (FQ).

Métodos Foram utilizadas medições repetidas de FEV₁ (3 meses a 5 anos de intervalo) de crianças saudáveis do repositório de dados da *Global Lung Function Initiative* para obter uma pontuação de variação condicional. Foram utilizados espirometria e os dados clínicos de uma base de dados clínicos de FQ para verificar a utilidade na prática clínica.

Resultados Derivou-se uma pontuação da variação de reprodutibilidade a partir de 47938 medições de FEV₁ em 7885 crianças saudáveis entre os 6 e os 18 anos. O algoritmo simples, que é condicionado pela medição inicial, também contabiliza a idade e o intervalo de tempo entre as medições. Os limites da pontuação da variação de reprodutibilidade foram muito mais estreitos do que os *cut-off* atualmente utilizados. Mais especificamente, as variações, consideradas como melhorias utilizando tanto uma variação relativa de 12% como de 10% em relação ao início do estudo, são demasiado amplas para crianças. Em casos de FQ, verificou-se um acordo geral entre as diferentes abordagens, com a vantagem distinta de que a pontuação da variação não foi enviesada pela regressão à média.

Conclusões Comparativamente às atuais abordagens à interpretação de medições repetidas da função pulmonar, a pontuação da variação proposta revelou-se menos enviesada e proporciona uma alternativa simples para reduzir os erros de interpretação.

INTRODUCTION

Forced expiratory volume in 1s (FEV₁), measured by spirometry, is an important predictor of respiratory morbidity and mortality.^{1–3} Consequently, FEV₁ is the primary biological measure used to assess the lung function status of individuals with respiratory diseases.⁴ An improvement in FEV₁ is also frequently used as an endpoint to assess the efficacy of interventional treatments.^{5–7}

Monitoring changes in lung function over time is important to evaluate disease progression and to monitor response to interventions. Current guidelines suggest a relative change in FEV₁ of greater than 12% from baseline and a 200mL absolute change in FEV₁ as a clinically meaningful change.⁴ This recommendation traced back to a 1981 review describing a significant deterioration from normal as a reduction greater than 1.65 times the coefficient of variation (CV) of repeated FEV₁ measurements in a healthy population.⁸ This commonly used cut-off corresponds to 90%

Key messages

What is the key question?

► What is a meaningful change in forced expiratory volume in 1 s (FEV₁) in children?

What is the bottom line?

► Current reproducibility limits for FEV₁ were derived from adult data and can lead to misinterpretation of results in children. We derive a change score for FEV₁ based on a large dataset of healthy children that can be used to more accurately interpret serial FEV₁ measurements.

Why read on?

► Measurement of lung function is integral to the management of children with respiratory conditions. A less biased and more accurate approach to defining a meaningful change can help to guide treatment and management decisions.

limits of reproducibility and a 10% false positive rate. In the 1976 study cited by the review, the CV was derived from weekly measurements of FEV₁ in 20 adult subjects (10 nonsmokers, 10 smokers)⁹; no children were included.

More recently, Kirkby *et al* define FEV₁ annual reproducibility in nearly 1000 healthy 9-year-old children as an absolute change within ± 1.3 z-scores.¹⁰ It is not clear whether these limits apply across the paediatric age range or for intervals shorter or longer than 1 year. Previous studies in children have found the correlation between repeated measurements to decrease as the interval between measurements increase.^{11 12} Further these limits have yet to be implemented in clinical use.

In clinical care of patients with cystic fibrosis (CF), a change greater than 10% from baseline is often used as a threshold for a meaningful change and worsening of FEV₁ of 10% or more is commonly used as part of definitions of a pulmonary exacerbation (PEX).¹³ Whether a patient returns to 90% of baseline FEV₁ after treatment with antibiotic therapy is also typically defined as the threshold for treatment success. As lung function measurements are integral to monitor and manage respiratory conditions in children, there is a need to develop reproducibility standards based on large and representative samples of healthy children to improve the interpretation of visit to visit changes. The objectives of this study were to (1) define individual reproducibility limit for FEV₁ change that represents the normal within-subject variability of measurements in health and (2) evaluate whether these reproducibility limits can be used to effectively monitor lung function changes in children with CF.

METHODS

Data sources

Anonymised longitudinal spirometry measurements from healthy Caucasian children and adolescents (≤ 18) were obtained from the Global Lung Function Initiative (GLI) data repository (www.lungfunction.org). Spirometry in each dataset was performed according to contemporaneous standards. Subjects with at least two spirometry measurements, made at least 1 day apart were included. Measurements with missing anthropometric data (eg, height, sex) and implausible height measurements (eg, serial height measurements that decreased by more than 5 cm) were excluded.

Spirometry and clinical data from all paediatric patients (age range 3.8–17.9 years) captured within the Toronto CF database between 2009 and 2017 were obtained ($n=282$). Exclusions were the same as described in the healthy data and included the removal of visits less than 180 days prior to lung transplant. Treatment with intravenous antibiotics for respiratory indications was considered a physician defined PEx. Stable visits were defined as any clinical encounter that did not overlap with active treatment with either oral or intravenous antibiotics. A physician defined PEx was called an oPEx if treated with oral antibiotics or (iPEx) if treated with intravenous antibiotics, with the following restrictions: (1) minimum of 7 days of treatment, (2) maximum of 4 months of treatment for iPEx or 28 days for oPEx, (3) Minimum of 21 days between antibiotic courses (iPEx) to be considered independent events and (4) minimum of 1 day between oral and IV antibiotics to be considered separate events, otherwise the event was denoted an iPEx. The effects of antibiotic treatment were summarised as the change in FEV_1 from the start of antibiotic treatment (–7 days to 4 days) to the end of treatment (–7 to +7 days). PEx events treated with oral antibiotics were not considered as too few of these events had complete spirometry measurements at the start and end of treatment.

Participants (or parents/guardians) in each of the studies that contributed data provided informed consent for their data to be collected for the primary study. Permission from the study investigators was obtained to use these anonymised data sources for secondary analyses.

Interpretation of spirometry

ATS/ERS reproducibility: The average CV of repeated FEV_1 measurements was calculated as the SD of all FEV_1 measurements (% predicted) in an individual divided by the mean of all measurements in the individual to replicate the approach used by McCarthy *et al.*⁹ Per cent predicted was used instead of litres since FEV_1 increase as children grow, and therefore, the calculations are not equivalent in children. z-scores: FEV_1 z-scores ($zFEV_1$) for each visit were calculated using the GLI reference equations.¹⁴ A $zFEV_1$ indicates how many SD a measurement is from the predicted value. The absolute difference in $zFEV_1$ was calculated as ($zFEV_{1 \text{ current}} - zFEV_{1 \text{ initial}}$). Relative change in FEV_1 : A relative change in FEV_1 was defined as ($\text{initial } FEV_1 - \text{current } FEV_1$)/initial FEV_1 . Since FEV_1 (measured in litres) increases as children grow, relative change was calculated from the per cent predicted values which standardise measurements for height, age and sex. Per cent predicted was derived using the GLI reference equations.¹⁴

Change score

We developed a change score for lung function measurements based on the method originally proposed for the interpretation of serial anthropometric measurements in children.¹⁴

$$\text{Change Score} = \frac{zFEV_{1 \text{ tf}} - (r \times r zFEV_{1 \text{ initial}})}{\sqrt{1 - r^2}}$$

The change score summarises the range of values that can be expected between two repeated measurements in healthy individuals,

given the initial measurement. FEV_1 values measured in litres were converted to z-scores to adjust for the expected changes in lung function with normal growth and development. Once standardised we can assume that the change between repeated lung function measurements is constant, or that the difference between two measurements should be normally distributed around zero. Furthermore, repeated measurements in the same person will be correlated (r), such that the first measurement can inform the second; however, the correlation is not perfect ($r \neq 1$). In the case of lung function measurements, previous studies have shown that correlation between two measurements in the same individual is lower the longer the time interval between measurements.^{11,12} The variability of measurements between individuals also depends on age,¹⁵ therefore, the variability of measurements within an individual may also vary with age.

To estimate the correlation between repeated measurements (r), which is necessary to calculate a change score, we developed a linear equation using the Pearson correlation coefficient estimated from all pairwise measurements in the same individual. Estimates were obtained using bootstrapping to account for the extra uncertainty. Sensitivity analyses included removal of obvious outliers, removal of the first test occasion, limiting the observation to the first two test occasions or using integer ages.

The change score can be interpreted as a deterioration (negative change score) or improvement (positive change score). The further away the change score is from zero the less likely it is within the normal reproducibility limits. A change score within ± 1.96 is within the limits of normal and has an inherent 5% false positive rate. A change score within ± 1.65 would have a 10% false positive rate.

RESULTS

A total of 50 265 FEV_1 measurements from 9307 healthy individuals (5–18 years of age; 61% were less than 12 years) were obtained (figure 1). Less than 5% ($n=2327$) of measurements were excluded, the majority were ($n=1404$) were excluded because there was only a single lung function measurement available. The remaining 7885 subjects (table 1) had 47 938 FEV_1 measurements. On average each subject had six measurements (range: 2–13), with an average time interval between repeated measurements of 0.9 years (range: 1.2 months to 11 years). In total there were 156 723 paired measurements (eg, a subject with 4 FEV_1 measurements would contribute six visit pairs with varying age at first visit and time intervals between visits).

ATS/ERS reproducibility: The average CV between repeated FEV_1 measurements in the same individual was 5.2%, which results in a reproducibility range ($1.65 \times CV$) of $\pm 8.6\%$ and therefore lower than the currently recommended 12% relative change. z-scores: The average $zFEV_1$ (ie, how far each observation was from the distribution of healthy individuals in the GLI reference population)¹⁵ of the first measurement was 0.12 (SD=1.0), indicating good overall fit with the GLI population. The change in $zFEV_1$ between measurements ($zFEV_{1 \text{ current}} - zFEV_{1 \text{ initial}}$), was -0.02 , 95% limits of agreement -0.8 ; 1.2 (range -4.7 to 6.5).

There was also a correlation observed between the first ($zFEV_{1 \text{ initial}}$) and difference between two measurements (figure 2). A healthy individual with a higher initial value is more likely to have a lower measurement at the second visit, whereas someone with a lower initial value is more likely to have a higher value. Relative change in FEV_1 : A total of 89% of the healthy observations had a relative change from initial visit within $\pm 10\%$; however, children with lower initial values were more likely to have a change greater than 10% than children with values in the normal range, and children with higher FEV_1 % predicted values were more likely to have a drop greater than 10% (figure 3). Change score: The correlation between repeated FEV_1 measures in the same subject decreased with time (figure 4A).

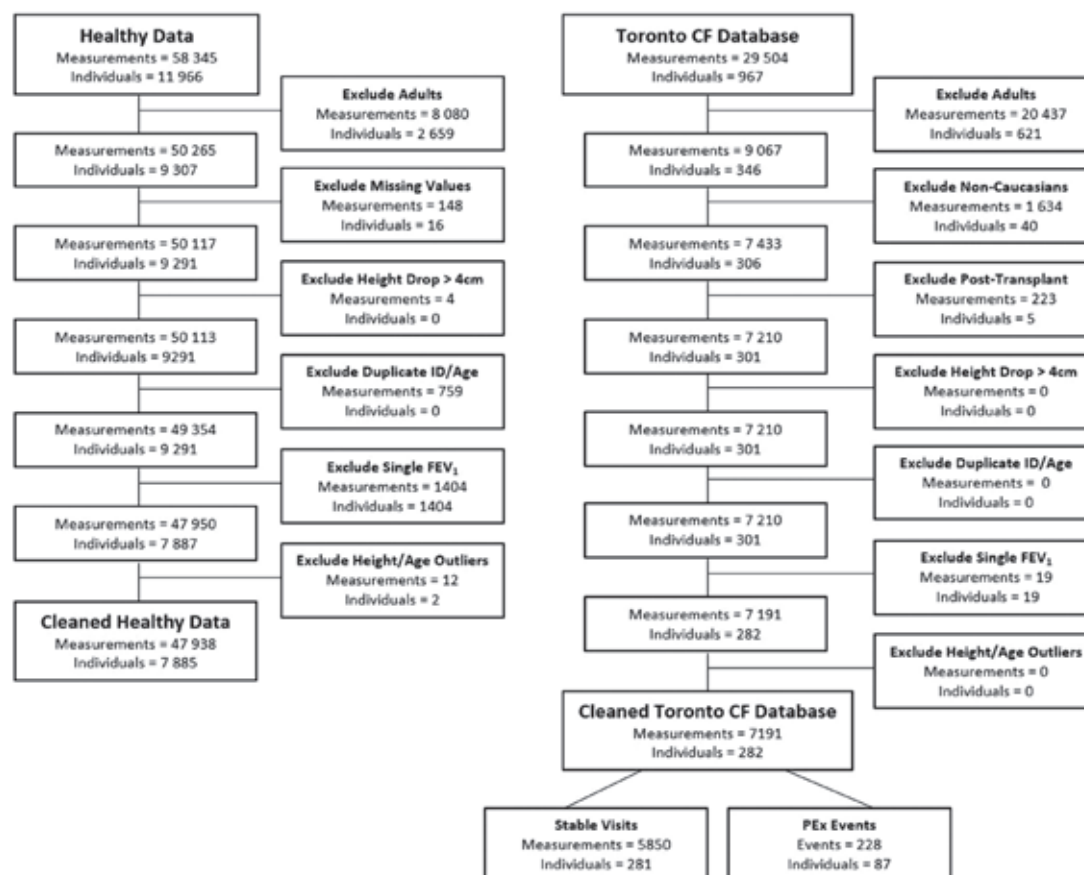


Figure 1 Flow diagram of study participants. CF, cystic fibrosis; FEV₁, forced expiratory volume in 1 s; PEX, pulmonary exacerbation.

Measurements made closer together in time were more correlated than those made further apart in time. Repeated measurements in young children were less correlated than repeated measurements in older children (figure 4B). In a multivariable regression analysis, both time and age were independently associated with the correlation between two measurements ($r=0.642$ (95% CI 0.62 to 0.66) -0.04 t years (95% CI -0.041 to -0.033) $+0.020$ a years (95% CI 0.018; 0.021)); where t is the time interval between measurements in years, and a is the initial age in years. The observed age and time-dependent correlation was consistent across multiple sensitivity analyses (online supplementary table S1 and online supplement figure S2).

The change score in the healthy individuals was normally distributed with a mean of -0.12 (SD 0.97), 96% of the change scores fell within ± 1.96 change scores (online supplementary figure S1). The change score was independent of the initial FEV₁ value (figure 5A).

Application in Cystic Fibrosis

A total of 282 subjects with CF in the Toronto CF database had 7191 FEV₁ measurements. On average each subject had 25 measurements (range: 2–106), with an average time inter-

val between repeated measurements of 2.2 months (range: 0.03 months to 5.8 years).

To illustrate how the change score could be used in practice we will consider a 6-year-old patient with CF who has an improvement in FEV₁ from 79% (-1.64 zFEV₁) to 92% predicted (-0.66 zFEV₁) between two annual visits ($r=0.686$). This corresponds to 16% relative increase, and a conditional z-score for change of 0.64, which is well within the limits of normal variability. In contrast a 14-year-old male patient (170cm) with a lung function drop from 90.6% (-0.78 zFEV₁) to 80.6% predicted (-1.60 zFEV₁) at 3 months ($r=0.907$), has a corresponding 11% relative drop and a conditional change score of -2.12 , which is outside the limits of normal variability. The same drop in lung function at a 4-year interval ($r=0.769$) corresponds to a conditional change ($Z_c=-1.56$) within the limits of normal variability.

Of the 7191 clinic visits (282 subjects) in the Toronto CF Database, 5850 were identified as stable. Each patient had an average of 17 stable clinical encounters (range: 2 to 93). The average length of time between all repeated stable measurements was 2.4 years (range 0.9 days to 8.9 years). Overall 75% of the visit-to-visit changes in FEV₁ between two stable visits (not treated with either oral or IV antibiotics) were within ± 1.96 change

Table 1 Demographics of symptomatic (V1) vs asymptomatic (C1)

	Healthy (n=7885)		CF (n=282)	
	Mean (SD)	Range	Mean (SD)	Range
Age at first measurement (years)	8.5 (1.9)	5.0–17.1	10.6 (3.1)	3.8–17.7
Height at first measurement (cm)	131.3 (12.4)	102.0–188.0	137.0 (23.3)	99.0–184.0
Height-for-age centile at first measurement (%)	54.0 (28.4)	0.02–100.0	32.9 (27.5)	0.05–96.3
No of FEV ₁ measurements	47 938		7191	
No of FEV ₁ measurements/subject	6.1 (3.0)	2.0–13.0	25.5 (20.9)	2.0–106.0
Time between successive measurements (years)	0.9 (0.7)	0.1–11.0	0.18 (0.17)	0.003–5.7
Time between first and last measurement (years)	4.6 (3.2)	0.2–12.0	4.5 (2.9)	0.04–8.9
Sex (individuals) n (%)	Female 3746 (47.5)	Male (%) 4139 (52.5)	Female (%) 147 (52.1)	Male (%) 135 (47.9)

CF, cystic fibrosis; FEV₁, forced expiratory volume in 1 s.

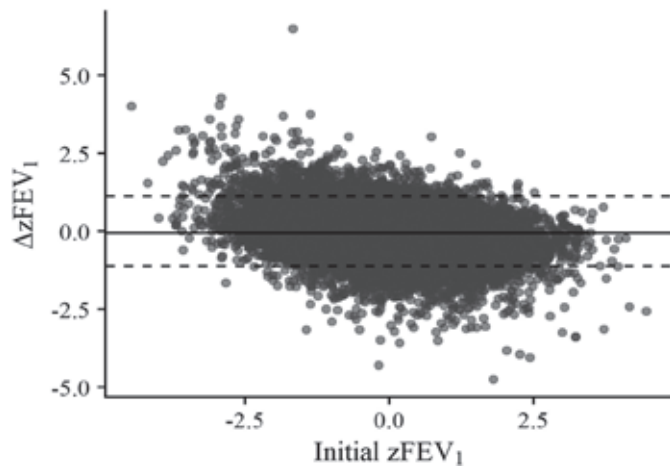


Figure 2 The change in FEV₁ between repeated measurements was strongly correlated with the initial measurement. There is a regression to the mean observed between repeated measurements. FEV₁, forced expiratory volume in 1 s; zFEV₁, FEV₁ z-score.

scores. The change score between stable visits was also constant across initial FEV₁ values (figure 6).

There were 228 PEx events (87 subjects) treated with IV antibiotics in the Toronto CF database with spirometry measurements at the start (−7 days to 4 days) and end of antibiotic therapy (−7 to +7 days). The average treatment duration was 16 days (range: 2.0–91.0 days). Of these events, 35% showed changes greater than a 10% relative change in % predicted FEV₁ and a change score greater than 1.96 units. An additional 37% did not show improvements with either a 10% relative change in FEV₁ % predicted nor the change score. Nearly one quarter (52/228) of visits had an improvement greater than 10% that were within 1.96 change scores.

DISCUSSION

Limits of reproducibility for FEV₁ were derived from a large dataset of healthy children to provide a standardised approach to interpretation of repeated lung function measurements. Currently used reproducibility limits for FEV₁ (eg, 12% relative change from baseline) are too wide for children and may miss important changes in lung function. In addition, fixed cut-offs (eg, 12% relative change or 10% relative change) of reproducibility are biased by the magnitude of the initial measurements such that children with lung function at the extremes of the range will have changes in lung function misinterpreted. The proposed change score is a simple algorithm that only requires knowledge of the two measured values converted to z-scores

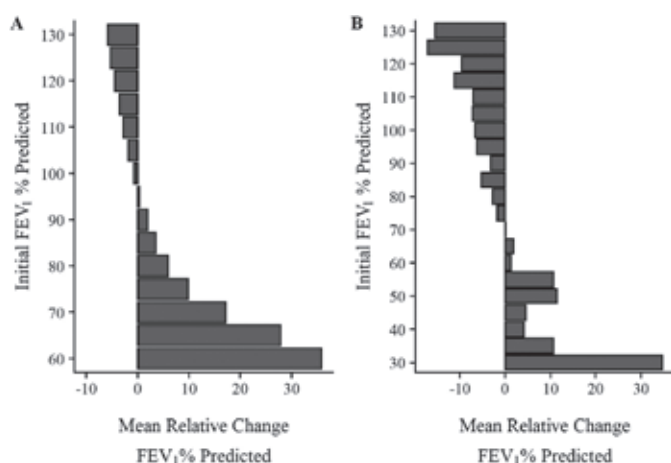


Figure 3 Waterfall plots of the relative change in FEV₁ % predicted in (A) healthy subjects and (B) children with CF averaged across groups of initial FEV₁. Between-visit change in FEV₁ was calculated from all within-patient pairwise measurements of individuals. FEV₁, forced expiratory volume in 1 s.

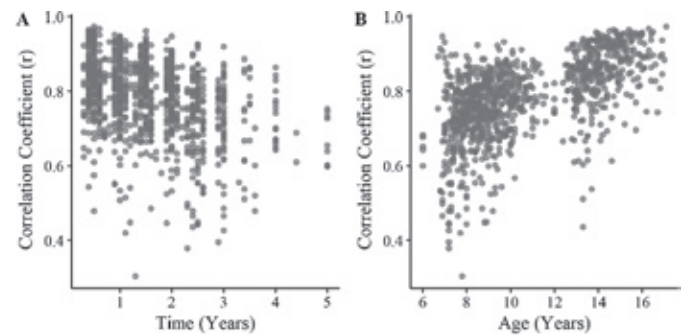


Figure 4 Correlations of repeated zFEV₁ measurements against A) time between measurements and B) age at the first measurement for 1015 pairs of correlations. FEV₁, forced expiratory volume in 1 s z-scores.

and the age of the subject at each visit. This information is readily available in pulmonary function test reports and the algorithm can easily be incorporated into trend reports.

Given the clinical need to track lung function over time for patients with respiratory diseases, a robust and unbiased measure to determine what constitutes meaningful changes is imperative. The use of a relative change in FEV₁ per cent predicted is the widespread standard, however, we observed that this measure is biased to extreme (high and low) FEV₁ values in both healthy children and children with CF. Consistent with previous literature, baseline lung function in both health and disease influences how much lung function declines with symptoms, and the magnitude of treatment response.^{12 16} This is particularly important for FEV₁ measurements in young children with CF, where lung function is both higher (often within the normal range) and more variable. These data also suggest that an improvement in FEV₁ of more than 10% from the start of antibiotic therapy may overestimate treatment response, as the observed changes were often within the reproducibility limits of FEV₁ defined by the change score. Together with the observation that healthy children with lower lung function are more likely to have improvements in lung function at the subsequent visit, the improvements seen following treatment after a drop in lung function may in part be explained by regression to the mean, and thus overestimate treatment response.

The decreasing correlation between repeated measurements in the same individual also has implications for how baseline lung function is defined, and therefore, whether there is a significant deterioration. People with CF are typically seen in clinic every 3 months, or during acute episodes of worsening. Lung function measurements from a stable visit within 3 months will be more closely correlated with the lung function measurement during the acute episode than a baseline measurement from 6 or 12 months before the episode. In some cases, the interval between stable visits may be much longer and the use of fixed cut-offs may impact the interpretation of visit to visit changes.

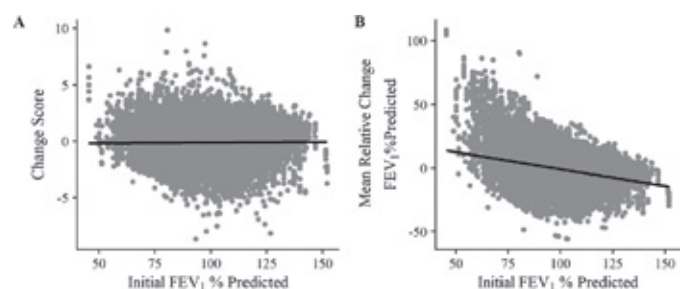


Figure 5 In healthy individuals, relationship between initial FEV₁ and (A) change score (linear mixed-effects regression 4.15–0.09*initial FEV₁) and (B) per cent predicted (linear mixed-effects regression 50.12–1.02*initial FEV₁). The change score is less influenced by initial value than relative change in FEV₁ per cent predicted. Regression coefficients centred at 50. FEV₁, forced expiratory volume in 1 s.

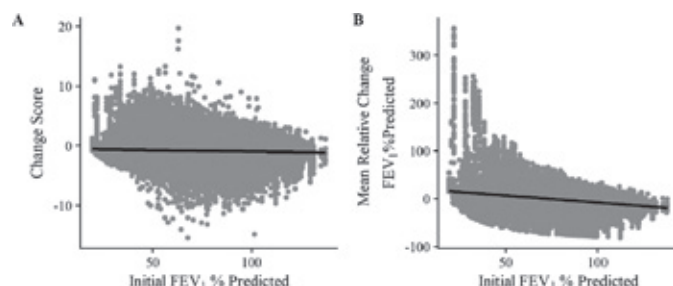


Figure 6 In stable CF, relationship between initial FEV₁ and (A) change score (linear mixed-effects regression $2.79 - 0.10 \times \text{initial FEV}_1$) and (B) per cent predicted (linear mixed-effects regression $45.38 - 1.35 \times \text{initial FEV}_1$). The change score is less influenced by initial value than relative change in FEV₁ per cent predicted. Regression coefficients centred at 50. CF, cystic fibrosis; FEV₁, forced expiratory volume in 1 s.

Another consideration is that the change score is a statistically derived cut-off that represents a false positive rate of 5%. The specific cut-point can be modified based on the patient group to identify the optimal trade-off between sensitivity and specificity for the specific context and pretest probability.

In children, the 12% ATS/ERS reproducibility limits are much wider than the limits calculated from this large dataset of repeated measurements in children.⁴ Further, the ATS/ERS limits and the change score are not directly comparable since the ATS/ERS limit of a 12% where the false positive rate is 10% and therefore not directly comparable to the 5% proposed by using 1.96 change scores. Recalculate the limits to be equivalent resulting in limits of reproducibility that are 10.2%, and still overestimate the range and not resolve the regression to the mean observed. Our results are consistent with previously reported reproducibility limits in children defined for 9-year-old children measured at a 1-year interval (range 9–16 months).¹⁰ The change score has the distinct advantage of spanning a much wider age range and time intervals and is conditional on the initial measurement.

There are several limitations to our approach that warrant discussion. First, the lack of repeated measurements in adults limits the use of the conditional change score to children only. We were unable to identify any longitudinal lung function data in adults with measurements made within intervals of less than 1 year. Furthermore, we were limited to data for FEV₁, which can be misleading in children if flow limitation is not achieved. The median FEV₁/FVC ratio in healthy children is above 0.8515 highlighting that most healthy children can expire nearly their total lung volume in approximately 1 s. Longitudinal data for FEV_{0.75} is needed to provide appropriate limits of reproducibility for children that cannot reach flow limitation.¹⁷ Alternatively, we need to identify more sensitive outcomes to measure lung function in children. Although the algorithm was developed using a large collection of healthy data in children, these data sets are not contemporaneous, such that they require validation in external datasets to confirm generalisability to current population characteristics, equipment and quality control methods. It is challenging to demonstrate that the conditional change score is superior to established limits of reproducibility as there is no clear gold standard. Use of a physician decision, such as whe-

ther or not to treat pulmonary symptoms with antibiotics, as a benchmark may be biased by indication and therefore not an ideal comparison. It will be necessary to prospectively evaluate whether tracking of lung function using this approach will result in long term improvements in outcomes. We used the GLI reference equations to calculate z-scores in order to account for the changes associated with lung growth during childhood. The simple algorithm can be applied to z-scores calculated from other reference equations. Ultimately reference equations derived from longitudinal data, where individual trajectories can be identified would be ideal; however, the practical and logistical considerations are not trivial.

DISCUSSION

The conditional change score for FEV₁ may help to facilitate interpretation of repeated lung function measurements in children to identify measurements that are outside the measurement variability observed in health. Once validated the relatively simple algorithm can be easily implemented into commercial software to facilitate monitoring of disease progression and to evaluate treatment response.

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Patient consent for publication Not required.

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Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository. Data are available on reasonable request. Healthy data are open access and available from the GLI Network data repository (www.lungfunction.org). Data from the Toronto CF database are available on reasonable request from the Hospital for Sick Children Research Ethics Board (ask.crs@sickkids.ca).

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ARTIGO ORIGINAL INVESTIGAÇÃO

Tabaco e *branding* nos filmes mais populares no Reino Unido de 2009 a 2017Alexander Barker,¹ Jo Cranwell,² Iona Fitzpatrick,³ Kathy Whittamore,¹ Khaldoon Alfayad,¹ Amira Haridy,¹ Rachael Murray,¹ John Britton¹¹Division of Epidemiology and Public Health, University of Nottingham, Nottingham, UK²Department for Health, University of Bath, Bath, UK³Tobacco Control Research Group (partner in Stopping Tobacco Organisations and Products), Department for Health, University of Bath, Bath, UK

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RESUMO

Contexto A exposição a conteúdo relacionado com tabaco em filmes é uma causa do consumo de tabaco por jovens. Num estudo anterior, referimos que o conteúdo relacionado com tabaco ocorreu em 70% de filmes populares de bilheteira no Reino Unido entre 1989 e 2008. Apresentamos agora uma análise do conteúdo relacionado com tabaco numa amostra dos filmes de grande sucesso de bilheteira no Reino Unido entre 2009 e 2017 e da exposição da população decorrente da exposição do espetador aos filmes de 2017.**Métodos** A ocorrência de intervalos de tabaco (uso real do tabaco, uso implícito, existência de parafernália para fumar ou *branding*) foi medida por uma codificação de intervalos de 5 minutos nos 15 filmes com maior sucesso comercial no Reino Unido, em cada ano entre 2009 e 2017. Foi utilizado um inquérito de representação nacional para estimar a exposição da população aos 15 filmes de maior sucesso no Reino Unido de 2017.**Resultados** Codificámos 3248 intervalos a partir de 135 filmes. O conteúdo relacionado com tabaco apareceu em 245 intervalos (8%, 95% IC 7% a 9%) em 56 (41%, 95% IC 33% a 49%) filmes. O conteúdo relacionado com tabaco surgiu em filmes de todas as classificações etárias BBFC e 36 (64%, 95% IC 51% a 77%) dos filmes contendo imagens de tabaco foram classificados como adequados para visualização por menores de 15 anos de idade. Embora com menor prevalência relativamente ao nosso estudo anterior, não se observaram evidências de declínio secular do conteúdo relacionado com tabaco durante este período de estudo. Os 15 principais filmes de 2017 produziram aproximadamente 21,6 (95% CI 21,06-22,14) milhões de impressões de tabaco a jovens entre os 10-18 anos de idade no Reino Unido.**Conclusões** O conteúdo relacionado com tabaco continua a surgir em filmes de bilheteira no Reino Unido e é amplamente visto pelos jovens, representando um dos principais motores do consumo de tabaco.

INTRODUCTION

Smoking is the largest avoidable cause of death and disability in rich countries, killing half of all lifelong smokers¹ and in 2018 causing an estimated 95 600 deaths and more than half a million hospital admissions in the UK.² Since most smokers in the UK begin regular smoking before reaching the age of 18 years,³ identifying and preventing causes of smoking uptake in these young people remain a public health priority.Exposure to tobacco imagery in film is a recognised cause of smoking uptake,⁴⁻⁶ and a meta-analysis of prospective cohort studies has estimated that children exposed to high levels of smoking imagery in film are more than 40% more likely to become smokers than those with little or no exposure.⁷ This exposure would be preventable through the age-classification systems that most countries apply to films if smoking and other tobacco imagery were considered harmful by regulators. In the UK, for example, age classification ratings are provided by the British Board of Film Classification (BBFC), whose mission includes protecting the public, and especially children, from content which might cause harm.⁸ The BBFC provide guidance to families to help them make informed decisions about what films are suitable for children. However, the BBFC does not appear to consider smoking to be harmful. In relation to smoking, BBFC guidelines state only that if smoking features to a significant extent in works which appeal to children, this will be indicated in information pro-

Key messages

What is the key question?

- Is tobacco content still prevalent in UK box office films?

What is the bottom line?

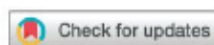
- Tobacco content continues to appear in UK box office films and is widely seen by young people, representing a major driver of smoking uptake.

Why read on?

- We present a content analysis of the annual top 15 grossing films at the UK box office between the years 2009 and 2017.

vided alongside the age classification and that, despite evidence that the effect of smoking is independent of film character type ('good guy or bad guy'), classification decisions only take into account promotion or glamorisation of smoking.⁹We have previously reported that 70% of 300 top-grossing UK cinema films in the years 1989–2008 included tobacco content and that 56% of those containing tobacco were rated as suitable for viewing by children aged under 15 years.¹⁰ To determine whether tobacco imagery continues to be prevalent in contemporary UK box office films, we now report an analysis of tobacco content in the top-grossing box office films distributed in the UK between 2009 and 2017 and estimate the population reach of this tobacco imagery in terms of UK audience impressions (the estimated number of times tobacco content was seen by an audience) to see how much of this content is being seen by young audience.

METHODS

Tobacco content in the 15 annual top grossing box office films in the UK for the years 2009–2017, identified from the British Film Industry Statistical Year Books,¹¹ was measured semiquantitatively using the 5 min interval coding method described previously.¹² Coding for each film began at the start of each film and continued until the end of the credits. In each interval, tobacco content was recorded in each of the following categories.**Actual tobacco use:** actual observed use of tobacco onscreen by any character, coded as cigarette, cigar, pipe or other (such as water pipe or chewing tobacco).**Implied tobacco use:** any implied tobacco use without any actual use onscreen (eg, holding a cigarette without actual smoking or a comment about going for a cigarette), coded as verbal or non-verbal.**Tobacco paraphernalia:** the presence of tobacco or tobacco-related materials, coded by the type of appearance (including cigarette or other tobacco pack, matches, lighter, ashtray, no smoking or smoking area signs).**Brand appearance:** The presence of clear and unambiguous tobacco branding, including cigarette or other tobacco packs, secondary advertising (advertisements appearing within other programmes) and branded merchandising.**Any tobacco content:** Any of the aforementioned.

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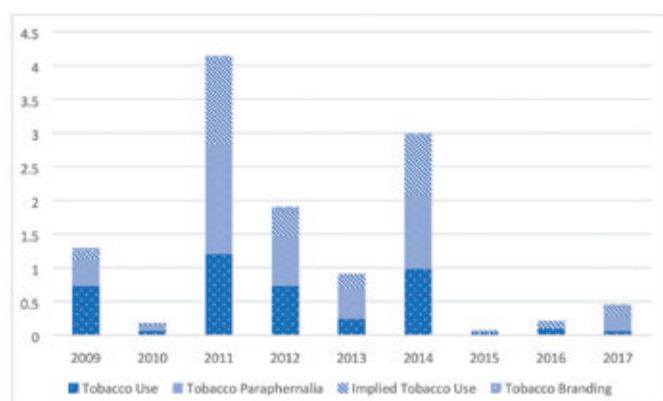


Figure 1 Trends in mean tobacco intervals per hour of film, 2009–2017.

For coding purposes, multiple instances of the same category in the same 5 min interval were considered to be single event, while instances that ran into consecutive 5 min periods were coded as separate events. Instances in different categories in the same interval were recorded as different events. Approximately 10% of all films were double coded and any discrepancies were discussed between coders and amended accordingly. Information on the age rating of each film was gained from the BBFC; information on the production of each film was gained from the Internet Movie Database.

To estimate exposure to a sample of films included in our content analysis, we included questions on viewing the 15 annual top grossing box office films in the UK for the year 2017 in a national survey of young people carried out by YouGov PLC. In accordance with YouGov practice, people aged 10–18 years were recruited by direct email invitations to a random sample of panellists from a database of individuals who had consented to be contacted. Consenting respondents then followed a link to an online survey where they were asked to indicate which of the 15 films they had seen. We then combined our estimates of tobacco imagery content in the films seen with UK mid-year population estimates for 201813 to estimate gross and per capita impressions, using previously reported methods.¹⁴ Dividing gross impressions by population mid-year estimates provided per capita impressions, the estimated number of tobacco impressions delivered to each person.

Coding data were entered directly on a Microsoft Excel (Version 16) spreadsheet as the films were watched and analysed using basic descriptive procedures and regression analysis in the Statistical Package for the Social Sciences (IBM SPSS V.24). Spearman's correlation was used to assess the relationship between the amount of tobacco intervals per hour of film over time. P values of <0.05 were deemed statistically significant.

RESULTS

The 135 films analysed totalled 265.2 hours (15 912 min) of film time, with a mean of 117.87 (SD 22.10) min/film, and a range from 82 min (*Secret Life of Pets*) to 174 min (*The Wolf of Wall Street*). The BBFC U, PG, 12/12A, 15 and 18 categories contained 17%, 16%, 50%, 14% and 2% of films, respectively. The majority of films analysed (59%, 95% CI 51% to 67%, 79/135) were produced solely in the USA. UK producers were involved in 25% (34/135) of films and were solely responsible for 3% (95% CI 1% to 5%, 4/135) of films. Other countries were involved in creating 17% (95% CI 11% to 23%, 23/135) of films. Only one film (*Taken 2*) had no UK or US production involvement.

There were 3248 5 min intervals in the films, with a mean of 24 per film, range 17–35. Tobacco content occurred in 245 intervals (8% of the total, 95% CI 7% to 9%) across 56 (41%, 95% CI 33% to 49%) films. The respective proportions of films containing any tobacco intervals in each of the BBFC age categories are shown in table 1.

Tobacco intervals occurred in 40% (95% CI 32% to 48%, 53/132) of all films rated suitable for watching by people aged under 18 years by the BBFC, as did 87% (95% CI 83% to 91% 214/245) of all tobacco intervals. Nearly two-thirds (64%, 95% CI 51% to 77%) of films containing tobacco imagery were classified as suitable for viewing by people aged under 15 years. Tobacco imagery occurred in 39% (95% CI 31% to 47%, 50/129) of films produced with some US involvement, and in all six (100%, 95% CI 100% to 100%) of those produced with no US involvement ($p=0.004$, Fisher's exact test).

The average number of intervals containing the different categories of tobacco content per hour of film varied from year to year, though not to a statistically significant extent and with no obvious trend. However, the mean number of tobacco intervals per hour of film has been particularly low since 2015 (figure 1).

Actual tobacco use occurred in 50% of all tobacco intervals (95% CI 44% to 56%, 123/245), in 24% of films (95% CI 17% to 31%, 32/135) and in a majority of cases (72 intervals, 59%, 95% CI 53% to 65%) involved cigarette smoking. Almost all (31/32) films featuring actual tobacco use were in BBFC 15 and lower categories, and more than half (56%, 95% CI 38% to 73%, 18/32) were rated suitable for audiences age 12 or lower. There was no clear trend in the frequency of tobacco intervals, or of intervals including tobacco use, per hour of film within BBFC age-classification categories, though there was no tobacco use in any U-rated film (figure 2). Tobacco use was much more common in films produced solely in the UK (occurring in 23 of 85 intervals, 28%, 95% CI 18% to 38%) than those produced in the US (49/1850 intervals, 3%, 95% CI 2% to 4%, $p<0.001$). Implied tobacco use occurred in 92 intervals (3%, 95% CI 2% to 4%, 92/3248) in 29 films (21%, 95% CI 14% to 28%, 29/135), typically in the form of non-verbal cues (83%, 95% CI 75% to 91%, 72/92). Tobacco paraphernalia occurred in 46 films (34%, 95% CI 26% to 42%, of all films) and in 4% of all intervals (95% CI 3% to 5%, 135/3248), typically in the form of ashtrays (alone or with other paraphernalia; 44% of paraphernalia intervals (95% CI 35% to 52%, 59/135), cigarette or other tobacco packs (12%, 95% CI 7% to 17%, 16/135), lighters (18%, 95% CI 17%–31%, 24/135) or matches (7%, 95% CI 3% to 11%, 10/135).

Tobacco branding, typically on tobacco packs, was present in seven intervals in six films. Five of these films were US productions, and one solely UK. Marlboro was the only brand to appear in more than one film, with Marlboro Gold appearing in two intervals in *Slumdog Millionaire* and Marlboro in a single interval in *The Amazing Spiderman*. More than one brand occurred in a single interval in *Men in Black 3* (Lucky Strike, Embassy). A fictional brand (Old Toby) appeared in one interval in *The Hobbit* and multiple fictional brands (Wellesley, Emperor and Carolina Menthol) in one interval in *IT* (table 2).

Trends over time

When the data from the current study were compared with the data from the previous study, the mean number of tobacco intervals per year are negatively correlated ($r(27)=-0.789$, $p<0.01$) (figure 3).

UK population exposure

Our YouGov Omnibus survey obtained data on which of the 15 2017 films sampled, four of which included tobacco content, had been seen by a nationally representative sample of 935 young people aged 10–18 years. The film with the most content, *IT*, was rated 15 and was seen by 26% (95% CI 23% to 28%) of young people aged 10–18 years in the UK. Using UK population estimates,¹⁵ we estimate that the four films delivered 21.6 (95% CI 21.06 to 22.14) million tobacco impressions to young people aged 10–18 years (table 3).

DISCUSSION

This study demonstrates that tobacco content, including tobacco smoking, continues to occur frequently in the most popular UK films; that this content is included in films in almost all age classification groups and that a majority of films containing smoking are classified by the BBFC as suitable for viewing by people aged under 15 years; and that tobacco imagery is significantly more likely to occur in films produced by UK companies. Although the proportion of films containing tobacco, at 40%, is much lower than the 70% we reported in an earlier analysis of films popular between 1989 and 2008,¹⁰ the proportion of films containing tobacco classified as suitable for viewing by people aged under 15 years was unchanged. Thus, while film makers may have reduced the amount of smoking imagery they include in films over the past decade, BBFC classification policy remains consistently passive in relation to this content,⁹ with classification decisions only taking into account promotion or glamorisation of smoking. Since there is strong causal evidence that exposure to tobacco imagery in films increases smoking uptake in adolescents,⁷ the BBFC thus continues to fail to meet its mission of protecting children from harmful content.⁸

Our study was limited by available coding resources to the top 15 most popular films each year, but these are likely to reflect the prominent pattern of tobacco exposure in films seen in UK cinemas each year since they typically represent around 50% or more of total annual box office takings.¹⁶ To code content in films, we used a method which has been widely used across a variety of audiovisual media^{12 14 16–24} and used double coding to ensure consistency between coders. Due to the lack of precise viewing figures, a nationally representative YouGov Omnibus survey was used to estimate the number of tobacco impressions delivered to a sample of the UK population. Our population exposure estimate included films from a single year, 2017; therefore, the UK population exposure to tobacco content in UK box

Table 1 Proportion of films in BBFC age category containing tobacco intervals

BBFC age rating*	Proportion of films in each age category containing tobacco intervals
U	1/23 (4%, 95% CI 0% to 12%)
PG	5/22 (23%, 95% CI 5% to 41%)
12/12A	30/68 (44% 95% CI 32% to 56%)
15	17/19 (89% 95% CI 75% to 100%)
18	3/3 (100%, 95% CI 100% to 100%)

*U, suitable for all ages; PG, parental guidance; 12/12A, suitable for 12 years and over; 15, suitable for 15 years and over; 18, suitable only for adults.
BBFC, British Board of Film Classification.

office films throughout the study period is thought to be much higher. The amount of tobacco content in films from 2017 was relatively low; our population estimate reflects this and would likely be higher for years with more tobacco content. Our tobacco exposure estimate is for the UK population, but these films are viewed worldwide, and therefore, UK population exposure figures probably represent a very small proportion of the true total global exposure. We used interval coding methods to generate semiquantitative measures of content over a standardised period of time to allow direct comparison between programmes which are shown for different amounts of time, therefore allowing an exploration of the percentage proportion of a programme. This method can lead to both underestimation (if high-frequency appearances are concentrated in short periods of time) and overestimation (if short appearances transition into two intervals) and has been widely used in previous studies.^{12 14 17 19–23 25–30} Alternative approaches such as frequency analysis,^{31–35} whereby all visual appearances are counted as individual events irrespective of duration, are available but assume that a single long appearance carries the same impact as a short appearance. Our estimate of population exposure is also based on 5 min intervals, rather than incidents, and therefore may be lower than estimates based on incidents alone.

While it is promising that tobacco content in films occurred less frequently during the present study period from 2009 to 2017, this

does not appear to reflect a secular trend; rather, our findings mirror those reported in US films in which the frequency of tobacco content declined to 2010 and then increased.³⁶ Furthermore, even at this lower level of occurrence, this content in UK films generates substantial population exposure, with films in a single year delivering 21.6 million tobacco impressions to young viewers. It is important to consider that many of these films were also released to an American audience. While there are differences in the age ratings between the UK and the USA, and the way that these ratings prevent young people from viewing content unsuitable for them, 17 films which were rated 15 in the UK were rated higher ('R') in the USA. In our population exposure, the film containing the most tobacco content and which delivered the most viewer impressions, IT was rated a 15 in the UK and an 'R' in the US. If the film had been given an adult (18) rating in the UK, this may have prevented this film from delivering a large proportion of tobacco impressions to young people.

Viewing habits are changing and online video-on-demand (VOD) services such as Netflix and Amazon Prime Instant Video, which allow users to watch whatever they choose at any time of day, are becoming increasingly popular.^{37–42} A number of films included in the present study are now featured on VOD services, thereby increasing exposure to tobacco content found in these films. These changes in the way that film content is consumed make it even more important that film classification authorities such as the BBFC follow WHO guidance, by prohibiting the appearance of branding in films and applying adult classifications to films containing tobacco imagery,⁴³ since film makers tailor content carefully to the requirements of their target age rating for each film. Knowing that including tobacco would ensure an adult rating in the global fourth largest national film market⁴⁴ would therefore be likely to result in widespread exclusion of tobacco imagery from all films aiming for a less than adult rating. We concede that due to changing viewing habits, a limitation of the current study is the focus on the top-15 UK box office films released annually in a cinema's, as these films as viewers can watch films from previous years on VOD services. Furthermore, a number of films and series are released exclusively on VOD services. Future studies should explore films on these services.

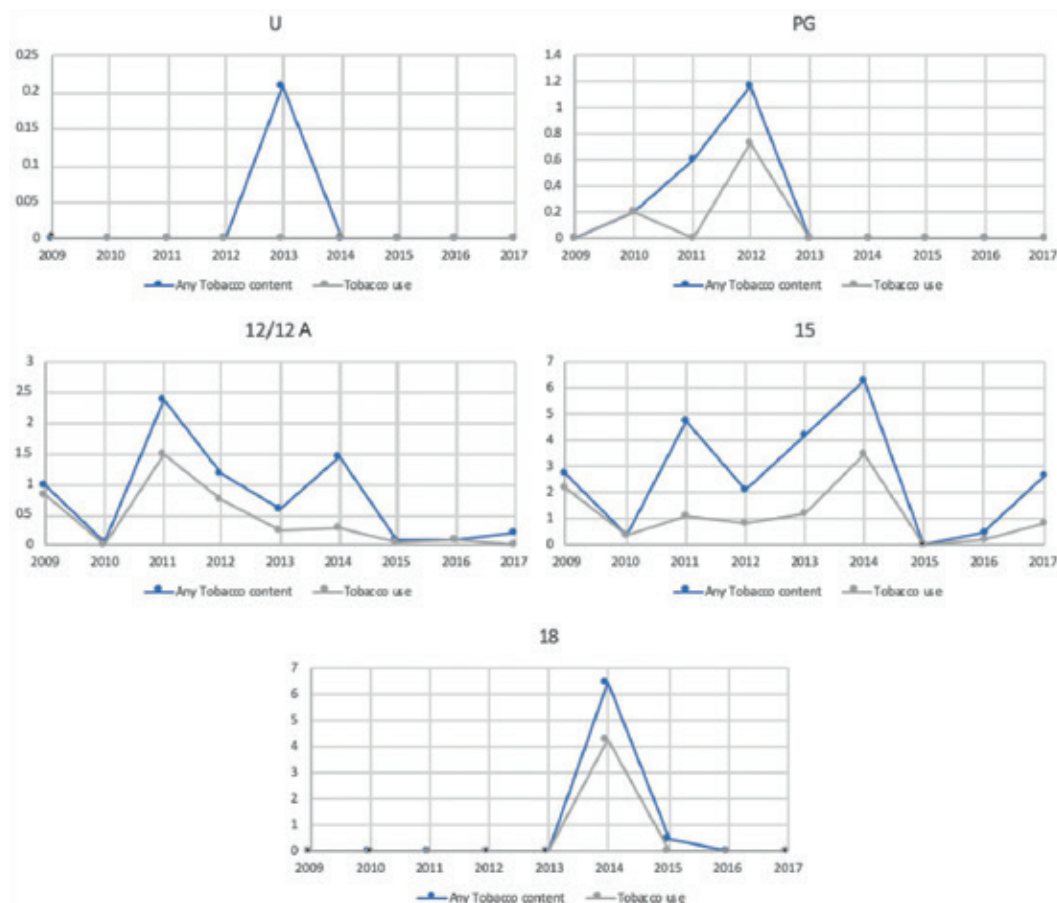


Figure 2 Trends in mean numbers of intervals containing any tobacco imagery, or tobacco use, per hour each year in relation to British Board of Film Classification category. There were no films rated 18 in the top UK box office films for 2009–2013. 12/12A, suitable for 12 years and over; 15, suitable for 15 years and over; 18, suitable only for adults; PG, parental guidance; U, suitable for all ages.

Table 2 Films containing tobacco branding

Title	Release year	Country of origin	Country of origin	Branding intervals, n	Brand(s)
Slumdog Millionaire	2009	UK	15	2	Marlboro (Gold)
Hangover II	2011	USA	15	1	K&J Lights
Amazing Spider Man	2012	USA	12	1	Marlboro
Men in Black 3	2012	USA	PG	1	Lucky Strike, Embassy
The Hobbit: An Unexpected Journey	2012	USA/NZ	12	1	Old Toby
IT	2017	USA/CANADA	15	1	llesley, Emperor, Carolina Menthol

BBFC, British Board of Film Classification.

Table 3 Estimated gross and per capita tobacco impressions delivered to 10–18 year olds in the UK from the four sampled films from 2017 containing tobacco imagery

Film	Age rating (BBFC)	Gross impressions (million)	95% CI	Per capita impressions	95% CI
IT	15	10.53	10.22 to 10.84	1.56	1.51 to 1.61
Spiderman: Homecoming	12a	6.21	6.09 to 6.33	0.92	0.90 to 0.94
Dunkirk	12a	1.35	1.30 to 1.40	0.2	0.19 to 0.21
Jumanji: Welcome to the Jungle	12a	3.51	3.45 to 3.57	0.52	0.51 to 0.53

BBFC, British Board of Film Classification.

The current study did not measure e-cigarette content; as e-cigarettes have become more popular over time, it is likely that this will be reflected in UK box office films. Future studies should explore the changing representation of tobacco products in films.

The current study thus provides further evidence in support of more effective UK implementation of the tobacco promotion policies outlined in the Framework Convention for Tobacco Control⁴⁵ to reduce youth exposure to smoking in movies. It also provides clear evidence that the BBFC has yet to deliver on its mission to protect children from this form of harmful imagery when they visit the cinema. Future tobacco content, whether glamorised or not, should be considered when assigning age classifications to films, and all films containing tobacco content should be assigned an adult (18) rating to protect children from this content.

Correction notice This article has been corrected since it was published Online First. References 27 and 30 have been removed as they do not refer to published work. The references have therefore been reordered to reflect the change. An acknowledgements statement has also been added to the paper.

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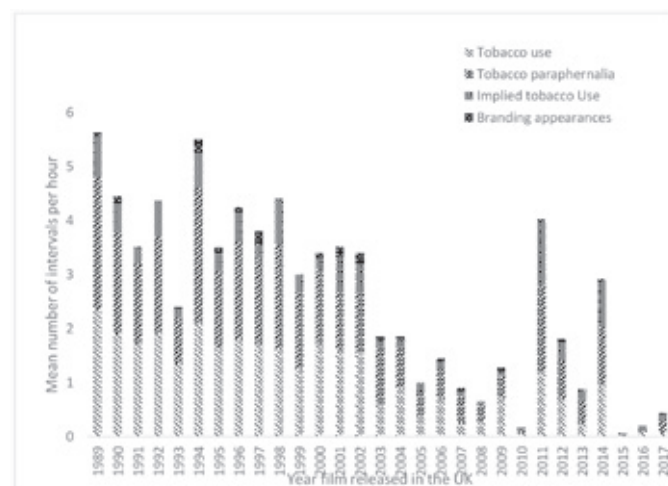
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Figure 3 Mean number of intervals containing tobacco content per hour of film, 1989–2017.

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Cuidado de doentes com DPOC e COVID-19: um ponto de vista para início de discussão

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INTRODUCTION

Coronavirus SARS-CoV-2 is currently causing a pandemic of COVID-19, with more than 3 million confirmed cases around the globe identified as of June 2020. During these extraordinary times, caring for patients with COVID-19 and underlying COPD poses particular challenges. Certain treatments relevant to treating patients with COPD, such as nebulised bronchodilators and noninvasive ventilation (NIV), are thought to carry an increased risk of viral spread via aerosols. Uncertainties on whether to use systemic steroids have entered the minds of intensive care and respiratory communities. Moreover, questions regarding which life-sustaining treatments to start, when to start them and even whether to start them are faced by clinicians on a daily basis. Treating COPD effectively in the context of COVID-19 is important since patients with COPD are at an increased risk of poor outcomes. Here, we summarise current viewpoints from four European countries on how to care for patients with COPD and COVID-19. We will address the following specific questions:

1. Are patients with COPD at an increased risk of COVID-19?
2. Should COVID-19 be considered a COPD exacerbation?
3. What is the optimal medical treatment for a patient with COPD and COVID-19?
4. Which ventilatory support should be provided to patients with COPD and COVID-19?

5. What other supportive treatments should be offered to patients with COPD and COVID-19?

6. How should end-of-life care be delivered in patients with COPD during the COVID-19 pandemic?

Are patients with COPD at an increased risk for COVID-19?

Since patients with COPD are vulnerable to viral respiratory tract infections, and COPD is generally a disease of the elderly, many had expected that patients with COPD would have a considerably increased risk of acquiring COVID-19. Studies so far, however, indicated only around 2% of patients admitted to hospital with COVID-19 infection in China had underlying COPD,^{1,2} while the prevalence of COPD in China ranges from 5% to 13%.³ Indeed, COPD was not the most commonly reported comorbidity seen in patients with COVID-19.¹ However, while the low percentage suggests COPD is not a risk factor for acquiring COVID-19, the size of the pandemic will still affect many patients with COPD. What's more, patients with COPD and COVID-19 have a worse clinical outcome compared with patients with other comorbidities²; patients with COPD and current smokers have an increased risk for severe disease.^{2,4} Moreover, both patients with COPD and smokers have an increased risk of dying from COVID-19.^{2,4}

Should a COVID-19 infection be considered a COPD exacerbation?

Coronaviruses are recognised seasonal causes of acute exacerbations of COPD (AECOPD). There remains controversy as to whether COVID-19 in a patient with underlying COPD should be considered a COPD exacerbation. This stems from our current definition of an exacerbation being a clinical diagnosis based on a change in symptoms needing a change in treatment.⁵ Thus, a patient with COVID-19 and COPD presenting with increased cough and breathlessness requiring treatment would fulfil the current definition of exacerbation. However, it is clear from imaging and postmortem studies that the pathology of a typical AECOPD is very different from the viral pneumonia typical of COVID-19.⁶ Thus, conceptually, COVID-19 in a patient with COPD is likely a very different pathophysiological process.

What is the medical treatment of a patient with COPD and COVID-19?

Though COVID-19 might not be a typical AECOPD, physicians must take the underlying COPD into consideration when treating COVID-19 in COPD. Also, diagnosing COVID-19 in a patient with COPD does not preclude a concomitant AECOPD and the need for treatment for this. Specific to treating patients with COPD is the necessity for bronchodilators, the beneficial effects of NIV and

the frequent need for antibiotics. Concerns have been raised as to whether and how these therapies should be offered to patients with COPD during the pandemic.

Antibiotics

Outside the context of COVID-19, not all AECOPDs should be treated with antibiotics,⁵ and current guidelines suggest reserving antibiotics for AECOPDs that require hospitalisation or ventilatory support.⁷ Overall, bacterial coinfections are uncommon in COVID-19: recent meta-analysis has shown that only 8% of patients had a bacterial/fungal coinfection.⁸ The risk of coinfections increases with the severity of COVID-19: a cohort study on risk factors for in-hospital death from COVID-19 found that 50% of non-survivors experienced secondary infections and that ventilatory-associated pneumonia was seen in 31%.⁹ Since it may be difficult to distinguish SARS-CoV-2 infections from a bacterial pneumonia and because patients with COPD are at risk for bacterial (super)infections, we suggest treating hospitalised patients with COPD and COVID-19 and respiratory symptoms with broad-spectrum antibiotics, guided by local/national guidelines for treating pneumonia. This is in line with the current WHO treatment guideline for severe COVID-19.¹⁰ Microbiological analysis, such as sputum culture, should be performed on admission and it may then be reasonable to stop antibiotics in the absence of a coinfection.

Bronchodilators and nebulisation

Bronchodilators are frequently given via nebuliser in hospitalised patients with COPD. The British Thoracic Society (BTS) guideline on treating patients with COPD and COVID-19 supports the use of nebulisers, claiming there is no evidence supporting an increased risk of viral transmission and, second, that aerosols surrounding the nebuliser come from the nebuliser not from patients.¹¹ However, the meta-analysis suggesting nebulisers do not increase viral transmission has some methodological concerns.¹² It is based on one study with a very small sample size, a second study investigating a variety of interventions and on a third in which infections began before exposure to nebulisation. The BTS guideline was also based on a methodological study showing that nebulisers predominantly produce aerosols not droplets, also used to suggest that nebulisation was safe.¹³ Viral transmission was not the subject of this investigation and since it remains open to debate whether droplets or aerosols can contain SARS-CoV-2, we do not think these results should be used as reassurance of no risk of transmission.

Alternative modes of inhalation are available, including pressurised metered-dose inhalers (pMDI) used with a spacer. In AECOPD pMDIs are not inferior to nebulisers.¹⁴ Long-acting dual bronchodilators may be preferred; some also have a fast onset of action, and are more effective with a longer duration of action. There are currently two long-acting pMDI combinations available which can be used with a spacer.

No maximum dosing has been provided for nebulised short-acting bronchodilators and very high doses are often administered for AECOPD. We suggest doubling the maximum maintenance dose of longacting bronchodilators, reflecting

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Quadro 1 Cuidado de doentes com DPOC e COVID-19

- 1 Não existem dados que sugiram que a DPOC seja um fator de risco para a contração da SARS-CoV-2.
- 2 Nos doentes com COVID-19, a DPOC está associada a um risco acrescido de maus resultados.
- 3 Uma infeção torácica por COVID-19 num indivíduo com DPOC subjacente é, provavelmente, um processo muito diferente de uma exacerbação aguda da DPOC. No entanto, o diagnóstico de COVID-19 não exclui uma exacerbação aguda de DPOC concomitante. Adicionalmente, o tratamento de COVID-19 deve ter em conta a DPOC subjacente.
- 4 Os antibióticos são aconselháveis em doentes com DPOC que necessitem de hospitalização por infeção torácica por SARS-CoV-2, especialmente quando é necessário suporte ventilatório.
- 5 Broncodilatadores administrados por pMDI e espaçador têm preferência relativamente ao tratamento nebulizador em doentes com DPOC e COVID-19 e sintomas respiratórios. Sugerimos a utilização de broncodilatadores de ação prolongada, se necessário com o dobro da frequência do tratamento de manutenção.
- 6 O tratamento com nebulizadores deve ser reservado aos doentes com doença potencialmente fatal ou a quem não possa utilizar um pMDI e um espaçador. Nesses casos, deve-se-á prestar atenção à transmissão por via aérea.
- 7 Recomenda-se um curso de corticosteróides sistémicos em doentes com DPOC e exacerbação aguda de DPOC que necessitem de hospitalização por infeção torácica por SARS-CoV-2.
- 8 Relativamente à escolha do suporte ventilatório, é de extrema importância que a vontade dos doentes e as decisões tomadas em relação ao suporte ventilatório e/ou a admissão e entubação na UCI sejam claras.
- 9 A VNI deve ser oferecida aos doentes com DPOC e COVID-19 e acidose respiratória hipercápnica aguda (crónica). Deve ter-se o cuidado de limitar a propagação viral com a utilização de máscaras não ventiladas, com o ar exalado a passar por um filtro bacteriano/viral antes de se entrar no quarto.
- 10 A VNI crónica deve ser continuada em doentes DPOC sob VNI domiciliária sempre que apresentem COVID-19. O tratamento domiciliário pode ser uma opção.
- 11 Sugerimos CNAF ou CPAP com FiO₂ elevadas em doentes com DPOC e COVID-19 e insuficiência respiratória hipoxémica aguda, em caso de insucesso da oxigenoterapia. Deve-se ter o cuidado de limitar a propagação viral utilizando máscaras cirúrgicas sobre as cânulas nasais. Com CPAP, a exalação pode ser filtrada antes de se entrar no quarto.
- 12 A intubação rápida e a ventilação mecânica invasiva devem ser providenciadas no caso de os doentes não responderem adequadamente ao suporte não invasivo, em função de discussões e decisões prévias sobre a escalada do tratamento.
- 13 Os doentes hospitalizados com DPOC e COVID-19 devem ser monitorizados quanto à perda de peso involuntária, devendo ser oferecido apoio dietético em conformidade.
- 14 A utilização de técnicas de desobstrução das vias aéreas em doentes com DPOC e COVID-19 deve ser fornecida com prudência para reduzir o risco de transmissão viral.
- 15 A mobilização precoce em doentes com DPOC e COVID-19 é muito importante.
- 16 É importante oferecer apoio psicológico e espiritual aos doentes com DPOC e COVID-19 durante a admissão hospitalar, bem como durante o acompanhamento.
- 17 A reabilitação pulmonar deve ser oferecida a todos os doentes com DPOC e COVID-19 após a alta hospitalar, podendo ter início de uma forma alternativa, desde que o distanciamento social ainda seja necessário.
- 18 Sugerimos o rastreio de todos os doentes com COVID-19, especialmente após a estadia na UCI, para limitações emocionais e funcionais e para oferecer reabilitação quando indicado.
- 19 O planeamento atempado de cuidados em doentes com DPOC deve ser fornecido, incluindo a comunicação entre o doente e o médico sobre os valores, objetivos e preferências dos doentes em relação a tratamentos de sustentação de vida, bem como abordar as suas preocupações sobre a fase da morte e as opções de cuidados paliativos. A oportunidade e a diligência nesta matéria são ainda mais importantes e desafiantes durante este período de pandemia de COVID-19.
- 20 A gestão adequada dos sintomas no final da vida em doentes com DPOC e COVID-19 é fundamental, incluindo a gestão da ansiedade, dispneia e sedação paliativa, conforme necessário.
- 21 Sugerimos que se considere a prestação de cuidados de luto aos familiares de doentes falecidos com DPOC e COVID-19, uma vez que estes podem incorrer em risco acrescido de luto complicado.

CNAF, cânulas nasais de alto fluxo; UCI, unidade de cuidados intensivos; VNI, ventilação não invasiva; pMDI, inaladores pressurizados doseáveis.

the high doses of short-acting bronchodilators often used in clinical practice. Since the safety of nebulisers is controversial and given that there is a suitable alternative, we recommend bronchodilators administered by pMDI and spacer over the use of nebuliser treatment in symptomatic patients with COPD and COVID-19. Nebulised treatment should be reserved for those situations in which pMDI with spacer is not possible, such as patients with severe, life-threatening disease or those unable to use a pMDI. For healthcare workers, respiratory masks (FFP-3 or equivalent) and other personnel protective equipment should be used during aerosol-generating procedures such as nebulisers.¹⁵

Systemic corticosteroids

It is recognised that not all AECOPDs need to be treated with systemic corticosteroids.⁵ Eosinophil-based steroid treatment has been advocated for both stable COPD and AECOPD; however, the use of this strategy in patients with COPD and COVID-19 has not been tested. Until recently, the efficacy of corticosteroids in general for treating COVID-19 was inconclusive, though a cohort study suggested steroids might improve clinical outcome in patients with COVID-19.¹⁶ Recent, preliminary results from the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial have shown that dexamethasone improves mortality in patients with COVID-19 requiring respiratory support.¹⁷ The WHO recommended against the use of steroids previously,¹⁰ but is now updating treatment guidelines to include dexamethasone or other corticosteroids.

Corticosteroids are beneficial to patients with severe AECOPD, especially in patients requiring ventilatory support, in whom steroids reduce ventilation days and NIV failure;

therefore, it is reasonable to treat patients with COPD and severe COVID-19 with course of corticosteroids. The RECOVERY regimen of 6 mg once daily could be used until more evidence is provided to guide treatment in patients with COPD with COVID-19.

Which ventilatory support should be provided to patients with COPD with respiratory failure?

Approximately, 14% of patients with a SARS-CoV-2 infection will develop severe disease requiring oxygen therapy and 5% will require transfer to the intensive care unit (ICU) and ventilatory support.⁵ In patients with COPD, several ventilatory support strategies can be considered, depending on the type of respiratory failure (ie, hypoxaemic or hypercapnic respiratory failure), and on local practice and availability of resources.¹⁸

Patients with hypoxaemic COPD and COVID-19 should be given controlled oxygen therapy as the first step.¹⁸ If hypoxaemia is insufficiently controlled with maximum oxygen supplementation, high-flow nasal cannula (HFNC) or CPAP with high oxygen flow should be considered. HFNC has recently been suggested as a management option in patients with COVID-19 with acute hypoxaemic respiratory failure.¹⁸ Reduction of hypercapnia and work of breathing might be additional benefits of HFNC in patients with COPD and COVID-19.^{19,20} However, HFNC is an open system and expiration cannot be filtered. A surgical mask can be placed over the nasal cannula to limit aerosol spread.¹⁵ Besides HFNC, CPAP with a high fraction of inspired oxygen (FiO₂) might be an option to treat hypoxaemic respiratory failure. CPAP provides a certain level of positive end-expiratory pressure, which might be

a useful add-on to oxygen supplementation. Furthermore, it is possible to filter expiration with CPAP and thus limit viral spread.

In patients with COPD with acute (on chronic) hypercapnic respiratory failure, NIV should be considered.²¹ There are no data showing that HFNC is equivalent and thus in this population we recommend using NIV first line. Transmission of virus can be reduced by using a nonvented mask with the exhaled air passing through a bacterial/viral filter before entering the room. Second, an expiration system with an active valve can be used and the oxygen supply can be connected close to the mask, so that a higher FiO₂ can be reached.²² Before starting NIV, the patient's willingness to undergo invasive mechanical ventilation (IMV), if NIV fails, should be discussed. Previous studies have shown that IMV after NIV failure is associated with higher mortality in AECOPD,²³ though this association has not been shown in COVID-19.²⁴

IMV should be instituted in patients with severe hypoxaemic respiratory failure or after NIV failure.¹⁸ Particularly in COPD, this decision should be made carefully, as it is known that in-hospital mortality with IMV in AECOPD is high.²⁵ Mortality is even higher for patients with COPD with severe COVID-19,² and the prolonged duration of mechanical ventilation seen in patients with COVID-19 might be particularly detrimental to the future health status of patients with COPD. In communicating IMV with patients with COPD, the risks and benefits should be explained clearly, and patients' wishes and preferences regarding life-prolonging therapies should be explored such that known risk factors for poor outcomes of IMV in COPD²⁶ can be weighed in a process of shared decision-making.

Finally, clinicians might be faced with patients on home mechanical ventilation admitted to the hospital with COVID-19. Their ventilatory support should be continued in hospital, with precautions to limit viral spread. Home treatment, supported by telemonitoring, might be preferred. The value and goals of a hospital admission should be discussed in the low likelihood of surviving a long period of ICU admission.

Which other supportive treatments should be offered to patients with COPD and COVID-19?

SARS-CoV-2 infections may have wideranging detrimental effects on patients' well-being. The strict isolation required may amplify feelings of solitude and hopelessness. Also, patients with SARS-CoV-2 often complain of loss of taste and appetite, increasing the risk of unintentional weight loss. Regular exercise, let alone rehabilitation, is difficult during a hospital stay.

Hospital treatment should therefore include dietary, as well as emotional and spiritual support. Early mobilisation is encouraged in recent COVID-19-specific physiotherapy guidelines, while airway clearance techniques should be provided prudently as they carry the risk of aerosol spread.²⁷ After discharge, discharge bundles should be continued to ensure smooth transfer from hospital to home care and to reduce the risk of readmission.⁵ Although pulmonary rehabilitation (PR) is recommended for people with COPD, rehabilitation in general should be offered to all patients with COVID-19 and certainly after ICU admission. The prolonged ICU stay is known to have significant impact on both physical and emotional well-being and patients may have accompanying symptoms of posttraumatic stress disorder.²⁸

Social distancing and concerns about residual viral transmission may limit possibilities for centre-based PR and physiotherapy. Home-based, unsupervised PR might be a solution in these times of social distancing.⁵ However, exercise-induced desaturation and cardiac arrhythmias associated with COVID-19 may make it difficult to guarantee the safety of unsupervised training. As soon as centre-based PR is possible, patients should again flow into such supervised programmes for optimal benefit.

How should end-of-life care be delivered in patients with COPD during the COVID-19 pandemic?

As described above, patients with COPD are at an increased risk for a poor outcome with COVID-19 and may choose to forego life-sustaining treatments. Ideally, identifying and discussing goals and preferences for future medical treatment and care, known as advance care planning (ACP), should have been undertaken before hospital admission. In practice, ACP is uncommon in COPD.⁵ The challenge in the current SARS-CoV-2 pandemic is addressing palliative care needs in times of crisis, at a time when preventing unwanted life-sustaining treatments is paramount. We stress that discussions concerning triage for intensive care treatment under resource scarcity should not be included in this process of ACP.

ACP also includes communication about end-of-life care. We advise timely communication about end-of-life care.²⁹ Patients may have worries about suffocation and the process of dying. Fear is common in patients in respiratory distress and could be pharmacologically treated with anxiolytics, such as lorazepam.³⁰ Opioids such as morphine can be used to manage dyspnoea and should not be delayed to the dying phase.³⁰ In patients with suffering despite optimal symptom management, palliative sedation can be discussed with patients and their relatives. Care for relatives needs specific attention in the SARS-CoV-2 pandemic: social distancing limits hospital visits and the necessity of personal protective equipment imposes severe restraints on saying goodbye to loved ones, thereby increasing the risk for complicated grief. Therefore, bereavement care needs to be considered.

CONCLUSION

This article provides an overview on how to manage patients with COPD and COVID-19 during the SARS-CoV-2 pandemic. Key points have been summarised in table 1. Caring for patients with COPD and COVID-19 poses special challenges for healthcare workers. Not only are they faced with severely ill, often elderly, patients who can deteriorate rapidly and have a poor prognosis, they are working in an environment with increased risk of being infected themselves. The suggestions put forward in this article provide a framework for those working in such challenging conditions. We acknowledge that such a viewpoint provides a momentary snapshot of current clinical practice and evidence how to treat COVID-19 effectively in patients with COPD is limited. Knowledge of COVID-19 is rapidly accumulating; therefore, the discussion on how to best treat patients with COPD and COVID-19 should continue and we invite the respiratory community to share best practices online.

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A duração do curso inicial de antibióticos está associada a recidiva recorrente na bronquite bacteriana prolongada

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RESUMO

A bronquite bacteriana prolongada (BBP) é a principal causa de tosse produtiva crônica em jovens crianças de países desenvolvidos. Apesar da sua elevada prevalência, existe uma escassez de evidências para informar sobre a duração ótima do tratamento, o que conduz a variações na prática. A recidiva da tosse crônica é comum e a recidiva de BBP (>3 episódios em 12 meses) está associada a diagnóstico subsequente de bronquiectasias. Investigamos os fatores associados a qualquer recidiva (≥1 episódio em 12 meses) e a BBP recorrente em 66 crianças. Nenhum fator foi significativamente associado a qualquer recidiva. A duração do tratamento antibiótico inicial foi o único fator significativamente associado à BBP recorrente. As crianças que receberam antibióticos durante 6 semanas apresentaram uma menor probabilidade de desenvolver BBP recorrente do que as que receberam durante 2 semanas ($p=0,046$). Este é o primeiro estudo a demonstrar uma associação entre a duração do curso inicial de antibióticos e bronquiectasias futuras. É necessária a realização de estudos prospectivos para investigar esta associação.

INTRODUCTION

Protracted bacterial bronchitis (PBB) is caused by endobronchial infection and is a leading cause of chronic wet cough in young children. The original definition (now called PBB micro) was (1) history of chronic wet cough, (2) lower airway infection confirmed with bronchoalveolar lavage culture obtained during flexible bronchoscopy (FB-BAL) and (3) cough resolution following treatment with an oral antibiotic.¹ As FB-BAL is unnecessary in most children with uncomplicated PBB, an alternative definition (PBB clinical) was developed in which lower airway culture was replaced with: 'absence of symptoms or signs suggestive of another cause of wet cough'.¹ In 2008, the UK Paediatric Cough Guideline suggested the use of amoxicillin-clavulanate for 4–6 weeks.² This recommendation was based on expert opinion due to an absence of evidence at that time.

In 2012, a randomised controlled trial provided the first prospective evidence to support the use of oral amoxicillin-clavulanate with a 2-week duration producing higher rates of cough resolution than placebo.³ However, the rate of cough resolution in the treatment group was only 48%. This has led to many clinicians continuing to use longer courses. The incidence of chronic cough relapse in PBB has been reported as high as 76%¹ and children with recurrent PBB (>3 episodes/year) have an increased risk of a subsequent diagnosis of bronchiectasis.⁴ We undertook a retrospective cohort study using clinical records to determine the factors associated with any relapse and recurrent PBB.

METHODS

A cohort of 113 children with PBB who had been referred to the University Hospitals of

North Midlands NHS Trust between 2013 and 2017 was identified using the local paediatric respiratory service database. Inclusion criteria were the following: chronic (>4 weeks) wet cough, initial treatment with amoxicillin-clavulanate of any duration producing cough resolution, confirmed diagnosis of PBB clinical or PBB micro and follow-up for ≥12 months. To reduce cohort heterogeneity, we excluded those who did not achieved cough resolution with the initial antibiotic course ($n=10$), those prescribed an alternative antibiotic ($n=21$), those on antibiotic prophylaxis ($n=5$) and those in whom it was not possible to assess the number of relapses in the 12 months post-treatment ($n=11$). Univariate analysis was used to investigate the association between any relapse or recurrent PBB and age, sex, symptom duration, PBB subtype (clinical vs micro) and antibiotic duration. Stepwise logistic regression was then performed using the above factors as well as the presence of malacia, bacteriology results and virology results for children who underwent FB-BAL. When FB-BAL had been performed, lavages were obtained from six lobes (including lingular) and sent for semi-quantitative bacterial culture. Only moderate and heavy growths were recorded. The sample from the right middle or most affected lobe was also tested using an extended respiratory virus PCR panel. The Health Research Authority decision tool (<http://www.hra-decisiontools.org.uk/research>) confirmed this project was not research and so ethical approval was not sought.

RESULTS

At referral, 66 children (35 boys) had a median (IQR) age of 2.1 (1.2–3.6) years and cough duration of 7.0 (5.0–10.75) months. The initial course of amoxicillin-clavulanate was 2 ($n=29$), 3 ($n=2$), 4 ($n=7$) or 6 weeks ($n=28$). The diagnosis was PBB clinical in 24 and PBB-micro in 42 (see table 1). Sixty-one children had a chest radiograph within 2 months of referral. Twenty-seven were normal, 26 showed bronchial wall thickening and 8 had other minor abnormalities. Forty-eight children had undergone FB-BAL. Forty-two (88%) children had ≥1 bacteria cultured and 11 (23%) had ≥1 virus identified. Polymicrobial was common. Full bacteriology and virology results are shown in online supplementary appendix 1. Nine children (19%) had airway malacia. Twelve (18%) children had CT chest, with a mean (IQR) duration from referral to scan of 1.1 (0.7–1.5) years. Two (3%) scans showed bronchiectasis. Of these two, one was treated initially with antibiotics for 2 weeks and one for 6 weeks. Both developed recurrent PBB. In the 12 months post-treatment, 45 (68%) children had a relapse and 20 (30%) had recurrent PBB (see table 1). The duration of antibiotics used to treat relapses varied between 2 and 6 weeks.



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Table 1 Films containing tobacco branding

Antibiotic duration, weeks	Pbb subtype, % (n)		Any relapse, % (n)		Recurrent Pbb, % (n)	
	Clinical	Micro	Yes	No	Yes	No
2	59 (17)	11 (12)	69 (20)	31 (9)	45 (13)	55 (16)
3-4	22 (2)	78 (7)	78 (7)	22 (2)	33 (3)	67 (6)
6	18 (5)	82 (23)	64 (18)	36 (10)	14 (4)	86 (24)
Total	36 (24)	62 (42)	68 (45)	32 (21)	30 (20)	70 (46)

PBB, protracted bacterial bronchitis.

Due to small numbers, children who received 3 or 4 weeks of treatment with amoxicillin–clavulanate were combined into one group for the statistical analysis. Univariate analysis did not find any factor to be significantly associated with any relapse. Antibiotic duration (6 weeks vs 2 weeks) was the only factor significantly associated with recurrent PBB ($p=0.046$) (see table 2). Using stepwise logistic regression with an entry/exit threshold of $p=0.1$, the only predictive factors for recurrent PBB were antibiotic duration (6 weeks vs 2 weeks) (OR: 0.115, CI: 0.026 to 0.509, $p=0.019$) and PBB clinical versus PBB micro (OR: 0.281, CI: 0.070 to 1.117, $p=0.071$).

DISCUSSION

To our knowledge, this is the first time cohort data have been used to identify the factors associated with any relapse and recurrent PBB. We found children who received 6 weeks of amoxicillin–clavulanate as their initial treatment were less likely to develop recurrent PBB than those who received 2 weeks. This finding is clinically important as recurrent PBB is associated with an increased risk of subsequent bronchiectasis. Lower cough relapse rates have previously been linked to longer durations of treatment.⁵ Recent international guidelines suggest starting with 2 weeks and if cough resolution does not occur, increasing to a maximum of 4 weeks. The rates of recurrent PBB were not significantly different between those who received 2 weeks of antibiotic and those who received 3–4 weeks but as the numbers in the latter group were small this should be interpreted with caution.

The variation in duration of initial antibiotic course seen in this cohort reflects the different practice of clinicians in our department and changes in practice and guidelines over time. As children were not randomised to different durations of treatment, cough severity may have influenced the clinician's choice of investigation and antibiotic duration. However, one would predict that more severely affected children with longer or more severe symptoms who undergo more invasive investigations would be most likely to be prescribed longer courses of antibiotics. It is surprising therefore that this group (children who were prescribed 6 weeks of antibiotic) had less recurrent PBB. A possible explanation for this finding is chronic cough relapse in PBB is caused by failed eradication of the original infection when shorter courses are used. Longer courses may be more likely to overcome biofilm resistance mechanisms of the causative endobronchial infection resulting in higher rates of

eradication and therefore less recurrent PBB. Longer antibiotic courses may also allow time the inflamed and denuded ciliated epithelium to recover which would be prevented by reinfection.

Although this is the second largest UK cohort study reported to date, we acknowledge that the relatively small sample size, particularly those treated with 3–4 weeks of antibiotic. The retrospective data collection also introduces potential bias. In particular, we relied on parental recall documented in notes or letters rather than objective measures of cough such as recording equipment or diaries. We collected data relating to the first episode of PBB treated at our centre, but it is possible we missed previous treatments in primary care. Our exclusion criteria also potentially introduced bias. Reassuringly, those excluded were similar to the included cohort in terms of median age (2.3 vs 2.1 years), median cough duration (7.5 vs 8.0 months), percentage receiving 6 weeks antibiotic (34% vs 42%) and percentage undergoing FB-BAL (57% vs 73%).

Longer courses of antibiotics are associated with increased cost, increased potential for adverse effects, increased risk of antibiotic resistance and poorer adherence. Any recommendation to use longer courses of antibiotics must therefore be supported by high-quality evidence. This study does not provide this level of evidence but does highlight the urgent need for a high-quality randomised trial comparing different durations of initial antibiotic treatment in children with suspected PBB.

Contributors EG-H collected the data, reviewed the drafts and approved the final version. WDC analysed the data, reviewed the drafts and approved the final version. NR undertook the statistical analysis and approved the final version. CG supervised the statistical analysis, reviewed the drafts and approved the final version. FJG conceptualised and designed the study, wrote the first draft, edited the drafts and approved the final version.

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Table 2 Univariate analysis assessing the impact of various factors on the incidence of any relapse and recurrent PBB

	Any relapse, n=66			Recurrent Pbb (>3 episodes/year), n=66		
	OR	95 IC	P value	OR	95 IC	P value
Age	0.892	0.709 to 1.121	0.327	0.952	0.740 to 1.225	0.702
Male versus female	0.784	0.276 to 2.226	0.648	0.346	0.116 to 1.033	0.057
Symptom duration	0.961	0.918 to 1.007	0.093	0.975	0.921 to 1.031	0.376
PBB clinical versus micro	0.369	0.126 to 1.079	0.069	0.667	0.216 to 2.053	0.480
Antibiotic duration (3–4 weeks vs 2 weeks)	1.575	0.272 to 9.131	0.510	0.615	0.128 to 2.950	0.694
Antibiotic duration (6 weeks vs 2 weeks)	0.810	0.269 to 2.441	0.463	0.205	0.057 to 0.743	0.046*

*Statistically significant association ($p<0.05$).

PBB, protracted bacterial bronchitis.

INSPIRA ESTABILIDADE¹ EXPIRA CONFIANÇA²



MAIOR ESTABILIDADE
NUMA ÚNICA TOMA.^{1,3}

O primeiro fôlego na DPOC.¹



LABA (LABA)



INALAÇÃO



1 VEZ AO DIA

Laventair
umeclidínio + vilanterol ELLIPTA
ELE PROTEGE

Um perfil de segurança comparável ao tiotrópio e ao tiotrópio/olodaterol.⁴⁻⁶

1) Maltais et al. Respir Res. 2019;20(1):238. Laventair demonstrou menor probabilidade de ocorrência de CID vs. salmeterol e umeclidínio. A CID é considerada um marcador da estabilidade da doença, e foi um endpoint secundário do estudo. 2) Van der Palen J et al. NPJ Prim Care Respir Med 2016 26:16079. Em doentes com DPOC, o inalador Ellipta mostrou menor ocorrência de erros críticos em relação a todos os outros inaladores avaliados. 3) RCM Laventair Ellipta, setembro 2019. 4) Feldman GJ et al. Adv Ther. 2017;34:2518-2533. 5) Maleki-Yazdi MR et al. Respir Med. 2014;108:1752-60. 6) Decramer M et al. Lancet Respir Med. 2014;2:472-86.

CID: deterioração clinicamente importante; DPOC: doença pulmonar obstrutiva crónica; LABA: Agonista β_2 de longa duração de ação; LAMA: Antagonista muscarínico de longa duração de ação.

INFORMAÇÕES ESSENCIAIS COMPATÍVEIS COM O RCM

▼ 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 sítio da internet do INFARMED: <http://www.infarmed.pt/web/infarmed/submissaooram>; E-mail: farmacovigilancia@infarmed.pt.

NOME DO MEDICAMENTO Laventair Ellipta **COMPOSIÇÃO QUALITATIVA E QUANTITATIVA** Cada inalação disponibiliza uma dose administrada de 65 microgramas de brometo de umeclidínio equivalente a 55 microgramas de umeclidínio e 22 microgramas de vilanterol (como trifrenatato). Isto corresponde a um recipiente unidose de 74,2 microgramas de brometo de umeclidínio equivalente a 62,5 microgramas de umeclidínio e 25 microgramas de vilanterol (como trifrenatato). **FORMA FARMACÉUTICA** Pó para inalação em recipiente unidose. **INDICAÇÕES TERAPÉUTICAS** Indicado como tratamento broncodilatador de manutenção para aliviar os sintomas em doentes adultos com doença pulmonar obstrutiva crónica (DPOC). **POSOLÓGIA E MODO DE ADMINISTRAÇÃO** Adultos A dose recomendada é uma inalação 1x/dia. Deve ser administrado à mesma hora do dia todos os dias para manter a broncodilação. A dose máxima é uma inalação 1x/dia. **Doentes idosos, Compromisso renal e Compromisso hepático ligeiro a moderado** Não é necessário ajustar a dose. Utilizar com precaução em doentes com compromisso hepático grave. **População pediátrica** Não existe utilização relevante na população pediátrica (<de 18 anos) para a indicação de DPOC. **Modo de administração** Via inalatória. **CONTRAINDICAÇÕES** Hipersensibilidade às substâncias ativas ou a qualquer um dos excipientes. **ADVERTÊNCIAS E PRECAUÇÕES ESPECIAIS DE UTILIZAÇÃO** **Asma:** Não deve ser utilizado em doentes com asma, não foi estudado nesta população. **Broncospasmo paradoxal:** Pode produzir broncospasmo paradoxal que pode colocar a vida em risco. O tratamento deve ser suspenso imediatamente e uma terapêutica alternativa instituída conforme o necessário. Não se destina a utilização aguda: Não está indicado para o tratamento de episódios agudos de broncospasmo. **Deterioração da doença:** O aumento da utilização de broncodilatadores de curta duração de ação para alívio dos sintomas indica deterioração do controlo. Na eventualidade de deterioração da DPOC durante o tratamento, deve realizar-se uma reavaliação ao doente e ao regime de tratamento da DPOC. **Efeitos cardiovasculares:** Podem ser vistos efeitos cardiovasculares, tais como arritmias cardíacas por ex., fibrilhação auricular e taquicardia. Deve ser utilizado com precaução em doentes com doença cardiovascular grave. **Atividade antimuscarínica:** Deve ser utilizado com precaução em doentes com retenção urinária ou com glaucoma de ângulo fechado. **Hipocaliemia:** A diminuição no potássio sérico é normalmente transitória, não necessitando de suplementação. Deve tomar-se precaução quando é utilizado com outros medicamentos que também têm o potencial para causar hipocaliemia. **Hiperglicemia:** Pode produzir hiperglicemia transitória em alguns doentes. Após o início do tratamento a glicose plasmática deve ser cuidadosamente monitorizada em doentes diabéticos. **Condições coexistentes:** Deve ser utilizado com precaução em doentes com perturbações convulsivas ou tirotóxicose e em doentes que respondem involuntariamente a agonistas beta, adrenérgicos. **Excipientes:** Cada dose contém aproximadamente 25 mg de lactose (na forma mono-hidratada). Doentes com problemas hereditários raros de intolerância à galactose, deficiência total de lactase ou malabsorção de glucose-galactose não devem utilizar este medicamento. **Efeitos indesejáveis** A reação adversa mais frequentemente notificada foi nasofaringite. **Infeções e infestações** **Frequentes** Infeção do trato urinário, sinusite, nasofaringite, faringite, infeção do trato respiratório superior **Doenças do sistema imunitário** **Pouco frequentes** Erupção cutânea **Raros** Anafilaxia, angioedema e urticária **Doenças do sistema nervoso** **Frequentes** Cefaleia **Pouco frequentes** Tremor, disgeusia **Desconhecido** Tonturas **Afeções oculares** **Raros** Visão turva, Glaucoma, Pressão intraocular aumentada **Doenças cardíacas** **Pouco frequentes** Fibrilhação auricular, taquicardia supraventricular, ritmo idioventricular, taquicardia, extra-sístoles supraventriculares, palpitações **Doenças respiratórias, torácicas e do mediastino** **Frequentes** Tosse, dor orofaríngea **Pouco frequentes** Disfonia **Raros** Broncospasmo paradoxal **Doenças gastrointestinais** **Frequentes** Obstipação, boca seca **Afeções dos tecidos cutâneos e subcutâneos** **Pouco frequentes** Erupção cutânea **Doenças renais e urinárias** **Raros** Retenção urinária, disúria, obstrução da saída da bexiga **TITULAR DA AIM** GlaxoSmithKline (Ireland) Limited, 12 Riverwalk, Citywest Business Campus, Dublin 24, Irlanda **DATA DA REVISÃO DO TEXTO** setembro 2019. **APRESENTAÇÃO:** Laventair Ellipta 55 mcg+22 mcg, 30 doses. **Regime de comparticipação:** Escalão B. Regime Geral 69%; Regime Especial 84%. **Medicamento Sujeito a Receita Médica.** Está disponível informação pormenorizada sobre este medicamento no sítio da internet da Agência Europeia de Medicamentos <http://www.ema.europa.eu/>. Consultar o RCM completo para informação detalhada. Medicamento sujeito a receita médica. Para mais informações e em caso de suspeita de um acontecimento adverso ou de outra informação de segurança, contactar o departamento médico da GlaxoSmithKline - +351 214129500. Para mais informações contactar o representante local do titular da AIM: Bial - Portela & Cª, S.A., À Av. da Siderurgia Nacional, 4745-457 S.Mamede do Coronado; NIF: 500220913. DDVSAM191018

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