

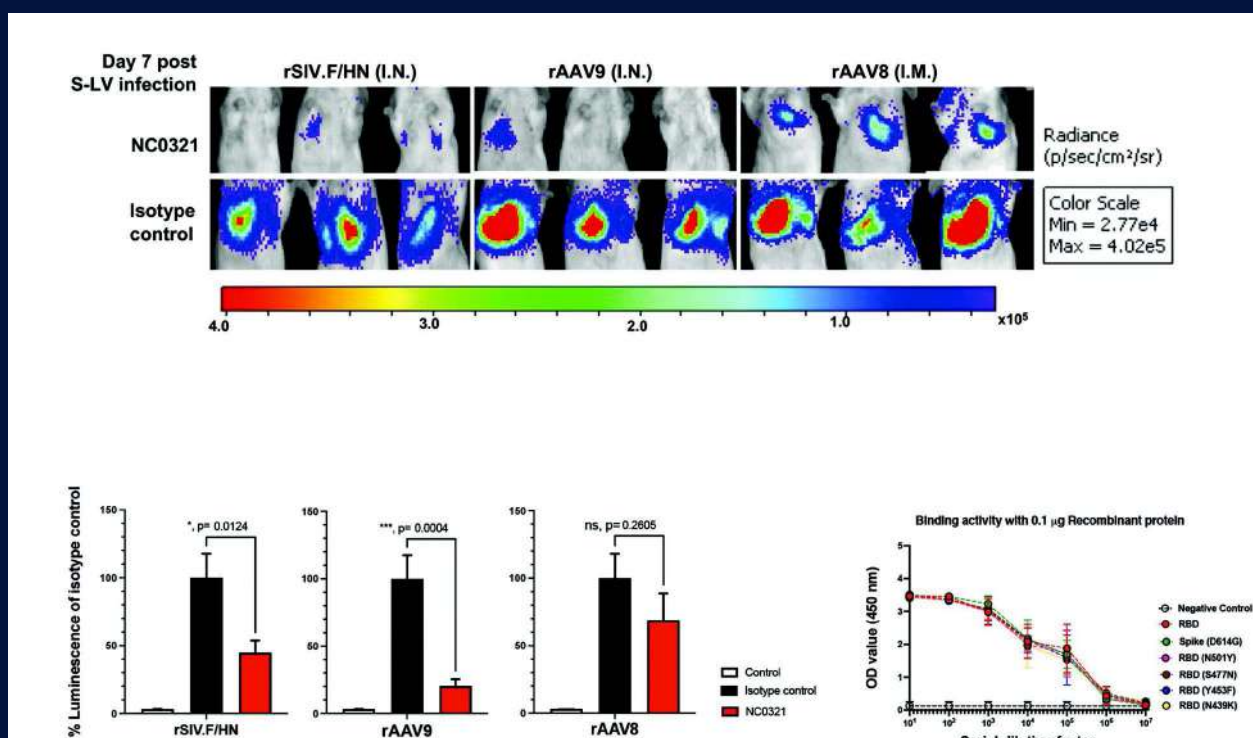
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1 INALAÇÃO¹



1 VEZ AO DIA¹



1 DISPOSITIVO¹

+171mL
(p<0,001)

MELHORIA SUPERIOR E CLINICAMENTE SIGNIFICATIVA DA FUNÇÃO PULMONAR vs. BUD/FOR Turbohaler²

-34%
(p<0,001)

REDUÇÃO SIGNIFICATIVA DA TAXA ANUAL DE EXACERBAÇÕES POR DPOC, ASSOCIADAS A HOSPITALIZAÇÕES vs. LAMA/LABA³

-42%
(p=0,01)

REDUÇÃO SIGNIFICATIVA DA MORTALIDADE POR TODAS AS CAUSAS (on-treatment) vs. LAMA/LABA^{3*}



Não foram registados novos dados relativos ao uso da associação em LAMA e um LABA.³

ELEBRATO
FUROATO DE FLUTICASONA | UMECLIDÍNIO | VILANTEROL | ELLIPTA
ELE RESPIRA

Referências: 1. RCM Elebrato Ellipta, julho de 2022; 2. Lipson DA et al. Am J Respir Crit Care Med 2017; 196:438–446; 3. Lipson DA et al. N Engl J Med 2018 378:1671–1680.

BUD: Budesonida; DPOC: Doença pulmonar obstrutiva crónica; FOR: Formoterol; ICS: Corticosteroide inalado; LABA: Agonista β2 de longa duração de ação; LAMA: Antagonista muscarínico de longa duração de ação.

*A mortalidade por todas as causas foi um endpoint exploratório do estudo IMPACT. Aqui, estão apresentados os dados on-treatment. Os eventos on-treatment são os que ocorreram desde o início de tratamento e até 7 dias após o seu término.

INFORMAÇÕES ESSENCIAIS COMPATÍVEIS COM O RCM

NOME DO MEDICAMENTO Elebrato Ellipta **COMPOSIÇÃO QUALITATIVA E QUANTITATIVA** Cada inalação disponibiliza uma dose administrada de 92 microgramas de furoato de fluticasona, 65 microgramas de brometo de umecliclínio equivalente a 55 microgramas de umecliclínio e 22 microgramas de vilanterol (como trifrenatato). Isto corresponde a um recipiente unidose de 100 microgramas de furoato de fluticasona, 74,2 microgramas de brometo de umecliclínio equivalente a 62,5 microgramas de umecliclínio e 25 microgramas de vilanterol (como trifrenatato). Excipiente com efeito conhecido: cada dose administrada contém aproximadamente 25 mg de lactose mono-hidratada. **FORMA FARMACÉUTICA** Pó para inalação em recipiente unidose **INDICAÇÕES TERAPÉUTICAS** Tratamento de manutenção em doentes adultos com doença pulmonar obstrutiva crónica (DPOC) moderada a grave, que não estejam adequadamente tratados com uma associação de um corticosteroide para inalação e um agonista beta-2 de longa duração de ação ou uma associação de um agonista beta-2 de longa duração de ação e um antagonista muscarínico de longa duração de ação (ver RCM para informação sobre efeitos sobre o controlo dos sintomas e prevenção das exacerbações). **POSOLOGIA E MODO DE ADMINISTRAÇÃO** A dose máxima recomendada é uma inalação 1x/dia, em cada dia à mesma hora. **Idosos, Compromisso renal e Compromisso hepático** Não é necessário ajustar a posologia. Utilizar com precaução em doentes com compromisso hepático moderado a grave. **População pediátrica** A utilização não é relevante na população pediátrica (<18 anos) para a indicação de DPOC. **Modo de administração** Via inalatória. **CONTRAINDICAÇÕES** Hipersensibilidade às substâncias ativas ou a qualquer um dos excipientes. **EFEITOS INDESEJÁVEIS** As reações adversas mais frequentemente notificadas são nasofaringite, cefaleia e infeção das vias respiratórias superiores. **Infeções e infestações** Frequentes: Pneumonia, infeção das vias respiratórias superiores, bronquite, faringite, rinite, sinusite, gripe, nasofaringite, candidíase da boca e da garganta e infeção do trato urinário. **Pouco frequentes:** Infeção viral das vias respiratórias superiores **Doenças do sistema imunitário** Raras Reações de hipersensibilidade, incluindo anafilaxia, angioedema, urticária e erupção cutânea **Doenças do sistema nervoso** Frequentes: Cefaleia **Pouco frequentes:** Disgeusia **Afeções oculares** **Pouco frequentes:** Visão turva, Glaucoma, Dor ocular Raros: Tensão intraocular aumentada **Cardiopatias** **Pouco frequentes:** Taquiarritmia supraventricular, taquicardia e fibrilhação auricular **Doenças respiratórias, torácicas e do mediastino** Frequentes: Tosse e dor orofaríngea **Pouco frequentes:** Disfonia **Doenças gastrointestinais** Frequentes: Obstipação **Pouco frequentes:** Boca seca **Afeções musculoesqueléticas e dos tecidos conjuntivos** Frequentes: Artralgia e dor no local de aplicação **Pouco frequentes:** Fraturas. **TITULAR DA AIM** GlaxoSmithKline Trading Services Limited, 12 Riverwalk, Citywest Business Campus, Dublin 24, Irlanda **DATA DA REVISÃO DO TEXTO** julho 22. **APRESENTAÇÃO:** Elebrato Ellipta 92 mcg+55 mcg+22mcg 30 doses. **Regime de Comparticipação:** Escalão B. Regime Geral 69%; Regime Especial 84%. 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. As Marcas Registadas são propriedade ou licenças das empresas do grupo GSK. ©2022 empresas do grupo GSK ou sob licença. DMgMA_PT220726

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Editorial

Estamos a chegar ao fim de 2022. Tal como se esperava, este ano foi marcado pelo início da retoma e da normalização da atividade clínica nos hospitais e centros de saúde do SNS, após os dois longos e penosos anos de maior incidência da pandemia Covid-19. No entanto, têm continuado a fazer-se sentir as enormes dificuldades que atravessa atualmente o SNS e as limitações que apresenta para lidar com as necessidades de saúde dos Portugueses, bastante mais notórias em certas regiões do País, onde os modelos de gestão desadequados e a carência de recursos humanos se fazem sentir mais. Como consequência disso, mal começa a estação mais fria e aumenta a procura de cuidados relacionados com as habituais infeções respiratórias próprias da estação, os serviços de urgência e as consultas abertas dos centros de saúde já não conseguem dar resposta à procura. Este fenómeno, que se repete anualmente há várias décadas, continua a não ser tratado de forma adequada e atempada pelos sucessivos responsáveis do Ministério da Saúde, para desespero de quem necessita utilizar os serviços de saúde.

Estamos, entretanto, de volta com mais um número da edição em língua Portuguesa de artigos selecionados das revistas *Thorax* e *Archives of Disease in Childhood*.

Desta vez, salientamos o interessante editorial sobre endotipagem da bronquiolite e avaliação do risco de asma que analisa vários estudos e conclui que, no futuro, a endotipagem de crianças com bronquiolite pode vir a ter um impacto significativo na prática clínica, permitindo a identificação precoce de pacientes que justifiquem um acompanhamento mais próximo devido a um maior risco de pieira e asma, e que possam ser tratados com estratégias preventivas ou terapêuticas específicas.

Um outro artigo selecionado “Sabe quando é que o inalador está vazio?” procurou avaliar se se os pacientes são capazes de identificar quando o inalador está vazio e se conhecem o método de eliminação do inalador. Verificou-se uma necessidade urgente de melhorar a tecnologia dos inaladores e de fornecer orientações adequadas sobre como identificar quando um IDC está vazio.

O artigo “Custo-eficácia da ventilação não-invasiva no domicílio em pacientes com DPOC”, comparou a relação custo-eficácia da VNI no domicílio com os cuidados habituais para duas populações com DPOC em fase terminal; uma população com DPOC estável a iniciar o tratamento sem internamento hospitalar recente; e uma população pós-hospitalar a iniciar o tratamento após internamento hospitalar devido a exacerbação e conclui que, provavelmente, a VNI ao domicílio é rentável para pacientes pós-hospitalização, mas há incerteza quanto à relação custo-eficácia da VNI ao domicílio em pacientes com DPOC estáveis

Chama-se ainda a atenção para um interessante artigo sobre investigação respiratória no Reino Unido e as oito ações-chave propostas pelos autores, das quais se salienta a recomendação para a criação de um observatório de monitorização para examinar os fatores de risco de doença respiratória e modelizar as mudanças previstas nos padrões de doença e a criação centros virtuais de excelência no Reino Unido para diferentes doenças respiratórias.

Finalmente, a carta “Características da sazonalidade transposta da epidemia de VSR no Reino Unido e na Irlanda em 2021: análise dos primeiros 10 000 pacientes” fala-nos do estudo BronchStart que é um estudo de coorte multicêntrico prospetivo que se propõe examinar o ressurgimento do VSR cuja sazonalidade foi perturbada pelas intervenções não farmacêuticas introduzidas globalmente para limitar a propagação do SARS-CoV-2.

Esperamos que esta seleção vos agrade e desejamos uma boa leitura.

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Da endotipagem da bronquiolite à avaliação do risco de asma

Silvia Carraro, Valentina Agnese Ferraro, Stefania Zanconato

A bronquiolite é a infecção mais comum das vias respiratórias inferiores em crianças mais novas e está associada a uma morbilidade significativa e a uma elevada taxa de hospitalização.¹ Adicionalmente, os dados epidemiológicos mostram que a bronquiolite durante o início da vida pode estar associada à morbilidade respiratória a longo prazo.² A identificação de crianças que irão apresentar sintomas respiratórios recorrentes após bronquiolite aguda representa um desafio de investigação com possível impacto significativo na prática clínica. Uma abordagem promissora para responder a esta questão de estudo deriva da aplicação de métodos estatísticos multivariados que podem gerir simultaneamente uma multiplicidade de dados obtidos a partir de diferentes fontes.

No seu estudo multicêntrico, Fujiogi *et al*³ analisaram dados recolhidos em 917 bebés (<1 ano de idade) hospitalizados por bronquiolite aguda em 17 centros norte-americanos participantes no 35º estudo *Multicenter Airway Research Collaboration*. Em crianças incluídas, foram recolhidos e analisados espécimes de vias aéreas nasofaríngeas, tanto através de abordagens lipídicas como transcriptómicas.

Aplicando uma análise de agrupamento consensual, os autores puderam classificar estas crianças de acordo com quatro endotipos, cada um definido por uma combinação variável de dados clínicos, virológicos e lipídicos. Graças à abordagem lipídica, os autores puderam estudar simultaneamente um grande número de lípidos, permitindo uma caracterização profunda dos bebés recrutados do ponto de vista metabólico. No entanto, o aspeto mais interessante do estudo é o uso integrado de dados lipídicos e clínicos para endotipar os pacientes. De facto, os dados bioquímicos metabólicos de um lado e os dados clínicos do outro fornecem informação complementar e, quando considerados em conjunto, podem oferecer uma classificação mais precisa dos pacientes. Do mesmo modo, um estudo recente realizado em pacientes com asma alérgica grave demonstrou que a construção de modelos que incluem dados clínicos e ómicos melhora a classificação dos pacientes, gerando um quadro mais completo do fenótipo dos pacientes.⁴ Ao lidar com condições multifatoriais complexas como a asma, a precisão e o rigor da caracterização dos pacientes é da maior importância, na medida em que pode lançar as bases para um tratamento personalizado.

Entre os quatro endotipos descritos em bebés com bronquiolite por Fujiogi *et al*,³ o endotipo A apresenta, do ponto de vista clínico, muitas das características típicas da bronquiolite clássica (idade mais jovem das

crianças, maior proporção de homens, maior prevalência de infecção por VRS, menor prevalência de problemas respiratórios e atopia na história pessoal, e menor prevalência de asma e eczema na família). Curiosamente, este endotipo foi caracterizado de um ponto de vista lipídico por um perfil lipídico misto, sem predomínio de um grupo específico de lípidos. O endotipo A foi, portanto, usado como referência na avaliação da associação de cada um dos três endotipos restantes com os resultados clínicos de interesse (pieira recorrente e asma). Através desta análise, os autores descobriram que apenas o endotipo D estava significativamente associado a pieira recorrente aos 3 anos de idade e à asma aos 6 anos de idade. Do ponto de vista clínico, os bebés com endotipo D caracterizaram-se por uma elevada proporção de história de problemas respiratórios, sensibilização ao eczema e IgE, elevada proporção de infecção por rinovírus e antecedentes familiares de asma e eczema. Do ponto de vista lipídico, comparativamente ao endotipo A, o endotipo D demonstrou níveis de esfingolípido e ácidos gordos polinsaturados mais reduzidos. Um estudo recente que analisou, através de abordagem metabólica, amostras séricas recolhidas de bebés pertencentes a duas coortes mãe-criança conduziu a resultados semelhantes, demonstrando que níveis reduzidos de ceramidas e esfingomielinas estavam associados a um aumento do risco de desenvolvimento de pieira/asma até aos 3 anos de idade.⁵ Considerados em conjunto, estes dados sugerem que um metabolismo desequilibrado dos esfingolípido pode ter um papel patogénico precoce na asma. Adicionalmente, em termos gerais, estes estudos destacam o papel potencial das abordagens ómicas na compreensão das vias metabólicas envolvidas numa doença multifatorial complexa como a asma.

A relação entre bronquiolite viral aguda na infância, pieira recorrente durante a idade pré-escolar e, eventualmente, o desenvolvimento de asma tem sido estudada há muito tempo, mas as ligações patogénicas entre estas condições ainda não foram completamente esclarecidas.

Em particular, a ligação entre a bronquiolite e a pieira recorrente tem sido debatida há muito tempo e têm sido sugeridas duas hipóteses principais: ou a bronquiolite viral aguda tem um papel causal e induz modificações nas vias respiratórias que favorecem a pieira recorrente ou ambas as condições são a expressão clínica de um contexto biológico comum (genético ou imunológico ou relacionado com a função das vias respiratórias).⁶

No contexto deste debate, um estudo recente do nosso grupo demonstrou que o perfil metabólico urinário à nascença não mostra qualquer associação com o desenvolvimento subsequente de bronquiolite aguda e pieira recorrente pós-bronquiolite, contestando a existência de um substrato bioquímico-meta-

bólico subjacente que predisponha a ambas as condições.⁸ Por outro lado, um estudo anterior que aplicou a mesma abordagem descreveu um perfil metabólico discriminante em bebés com bronquiolite viral aguda que, mais tarde, desenvolveram pieira recorrente.⁹ Considerados em conjunto, estes estudos sugerem que a análise metabólica, embora incapaz de identificar um perfil preditivo de pieira pós-bronquiolite no momento do nascimento, consegue captar a perturbação metabólica causada pela bronquiolite e associada à doença de pieira subsequente.

O artigo de Fujiogi *et al*,³ que classifica 917 bebés em quatro endotipos de acordo com as características clínicas, virológicas e lipídicas, e que mostra como os endotipos descritos possuem um risco diferente de desenvolvimento de pieira recorrente e asma, reforça a hipótese de que o esquema metabólico durante a infecção aguda poderia ser considerado conjuntamente com as características clínicas para estratificar as crianças de acordo com o risco de desenvolvimento de pieira e asma. No futuro próximo, a endotipagem de crianças com bronquiolite pode ter um impacto significativo na prática clínica, permitindo a identificação precoce de pacientes que justifiquem um acompanhamento mais próximo devido a um maior risco de pieira e asma, e que possam ser tratados com estratégias preventivas ou terapêuticas específicas.

São necessários mais estudos para testar a aplicabilidade dos endotipos propostos noutras populações independentes, assim como para seguir a trajetória lipídica ao longo do tempo após a infecção aguda, de modo a investigar mais profundamente as ligações patogénicas entre a bronquiolite e o subsequente desenvolvimento de sintomas respiratórios recorrentes.

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PCR de transcrição reversa de esfregaço de saliva oral para Covid-19 na população pediátrica

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RESUMO

Objetivos Avaliar o desempenho de PCR de transcrição reversa (RT-PCR) de esfregaço de saliva oral (ESO) em comparação com RT-PCR e teste de diagnóstico rápido de antígeno (Ag-RDT) em esfregaços nasofaríngeos (ENF) para a SARS-CoV-2 em crianças.

Desenho Estudo de diagnóstico multicêntrico transversal.

Contexto Estudo integrado numa coorte prospectiva e observacional (EPICO-AEP) realizado entre Fevereiro e Março de 2021, incluindo 10 hospitais em Espanha.

Pacientes Foram incluídas crianças dos 0 aos 18 anos com sintomas compatíveis com a Covid-19 de ≤5 dias de duração. Foram recolhidas duas amostras de ENF (Ag-RDT e RT-PCR) e uma amostra de ESO para RT-PCR.

Principal resultado Desempenho do Ag-RDT e RT-PCR em ENF e RT-PCR em amostra de ESO para SARS-CoV-2.

Resultados Foram incluídas 1174 crianças, com 3,8 anos de idade (IQR 1,7-9,0); 73/1174 (6,2%) pacientes com resultados positivos em pelo menos uma das técnicas. A sensibilidade e especificidade do ESO RT-PCR foram de 72,1% (95% IC 59,7 a 81,9) e 99,6% (95% IC 99 a 99,9), respetivamente, contra 61,8% (95% IC 49,1 a 73) e 99,9% (95% IC 99,4 a 100) para o Ag-RDT. O índice Kappa foi de 0,79 (95% IC 0,72 a 0,88) para o ESO RT-PCR e 0,74 (95% IC 0,65 a 0,84) para o Ag-RDT versus ENF RT-PCR.

Conclusões O RT-PCR na amostra ESO é uma opção precisa para testes de SARS-CoV-2 em crianças. Uma técnica menos intrusiva para pacientes mais jovens, que normalmente são testados com frequência, pode aumentar o número de pacientes testados.

INTRODUCTION

Nucleic acid amplification testing in nasopharyngeal swab (NPS) samples is considered as the gold standard technique for the diagnosis of SARS-CoV-2 infection¹; however, this technique requires trained staff, is associated with an increased risk of complications (epistaxis, retained swabs, cerebrospinal fluid leak),² is unpleasant and generates anxiety mainly in children. Indeed, patients with mild symptoms are often put off accessing the test.^{2,3}

Saliva swab reverse transcription PCR (RT-PCR) is an alternative and minimally invasive test for the diagnosis of SARS-CoV-2 infection. Data from a recent systematic review showed that given a proper RT-PCR kit is chosen, the accuracy of RT-PCR on saliva and NPS is similar, particularly in ambulatory patients,⁴ yet saliva tests have

Key messages

What is the key question?

- SARS-CoV-2 saliva tests have not been widely implemented in children.
- The accuracy of reverse transcription PCR (RT-PCR) on saliva and nasopharyngeal swab is similar.
- Studies in this population are scarce, particularly in preschoolers.

What is the bottom line?

- RT-PCR on oral saliva swab is an accurate option for SARS-CoV-2 testing in children.
- RT-PCR on oral saliva swab shows higher sensitivity than the antigen rapid diagnostic test on nasopharyngeal swab.

Why read on?

- Saliva swab may be more acceptable for younger patients than nasopharyngeal swab, possibly increasing the capacity of testing in this age group.
- Saliva swab could be added to the SARS-CoV-2 diagnostic protocols as an alternative specimen to nasopharyngeal swab in children.

not been widely implemented in children. Indeed, studies in this population are scarce, particularly in preschoolers.⁵⁻¹⁰

We performed this study with the hypothesis that oral saliva swab (OSS) RT-PCR is as sensitive as RT-PCR on NPS, which is considered the gold standard. Our objective was to analyse the performance of OSS RT-PCR in comparison to (1) the gold standard (RT-PCR on NPS) and (2) the Panbio SARS-CoV-2 antigen rapid test (Ag-RDT) on NPS, a technique widely implemented, in a symptomatic paediatric population evaluated at the emergency departments of 10 Spanish hospitals.

METHODS

Study design

Cross-sectional multicentre diagnostic study nested in a prospective, observational cohort, the



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Epidemiological Study of Covid-19 in Children of the Spanish Society of Pediatrics (EPICO-AEP). Participants were children from 0 to 18 years old with symptoms compatible with SARS-CoV-2 infection of ≤ 5 days of duration, seen in the emergency departments of 10 secondary and tertiary hospitals, in Madrid and Almería, Spain.

The study was performed between February and March 2021. At that time, the peak incidence of Covid-19 in Spain was 559/100 000 individuals.¹¹ Standards for Reporting Diagnostic Accuracy (STARD) 2015 guidelines for reporting diagnostic accuracy studies were followed throughout.¹²

SARS-CoV-2 testing

Trained nurses collected three samples consecutively from each patient following a standardised procedure: two NPS samples (for Ag-RDT and RT-PCR) and one OSS sample for RT-PCR. The Panbio SARS-CoV-2 Ag-RDT was purchased from Abbott Rapid Diagnostics (Jena, Germany). OSS samples were collected using the identical brand of the swab for the NPS samples. The procedure included smearing the swab under the tongue, between the gums and lips and in the inner part of both cheeks, but not the pharynx. Older patients were invited to cough with their mouths closed before sampling. A minimum amount of saliva was not necessary for the oral smear. Clinicians recommended patients not eat or drink at least 30 min before sampling. OSS and NPS to be used for RT-PCR were placed in standard viral transport media (Delta Labs, Barcelona, Spain).

The nurses in charge of collecting samples performed Ag-RDT on-site and results were interpreted following the manufacturer's instructions, whereas OSS and NPS for RT-PCR were immediately transported to each local microbiology laboratory of each participating centre after specimen collection.

RT-PCR testing in OSS and NPS was performed immediately after specimen collection, targeting at least two viral genomic fragments following the manufacturer's recommendations in each laboratory. RNA was extracted from samples by using the automated systems in place in each of the participating centres. OSS were processed using the same protocol as NPS in each centre. It was considered indeterminate those samples in which only one of the genes was amplified with a high cycle threshold (Ct). Turnaround time was less than 12 hours at all the centres. Nurses who interpreted the Ag-RDT did not have access to the RT-PCR result. Lab technicians had access to the Ag-RDT result. Clinicians attending each patient had the information of the three tests once available. Clinical information was available for all of them.

Patients with discordant diagnostic test results from any of the three different tests were invited to a second visit and a blood sample was drawn for SARS-CoV-2 IgG detection. Samples were performed in less than 24 hours after the researchers were aware of the results and less than 48 hours from the initial clinical visit. IgG antibodies directed against the SARS-CoV-2 surface S1 domain

of the spike protein or the internal nucleocapsid protein were measured in the serum samples using commercial enzyme-linked immunosorbent assay (ELISA) or chemiluminescent immunoassay kits, depending on availability in each centre following manufacturer's instructions. Besides, in these patients, a study of viral viability was performed whenever possible. All the information related to this additional analysis is included in the online supplemental material.

Data collection

Clinical and laboratory data were collected using RedCap electronic data capture tools^{13 14} hosted at the 12 de Octubre Hospital.

Statistical methods

The intended sample size was 1500 patients to estimate a 70% sensitivity for OSS and 90% of sensitivity for Ag-RDT to reach a statistical power of 80% with acceptable precision.

The study population was described using counts and percentages for categorical variables and medians and IQRs for continuous variables. Categorical variables were compared with χ^2 or Fisher's test, and continuous variables with Mann-Whitney U test. The performance of the test was evaluated estimating the sensitivity, specificity, negative and positive predictive values and the kappa index. Additionally, we provided the sensitivity and specificity of the different diagnostic techniques stratified by age (≤ 3 and > 3 years old). The performance of the test was evaluated by estimating the sensitivity, specificity, negative and positive predictive values and the kappa index taking RT-PCR on NPS as the gold standard. A confusion matrix was assessed to calculate the diagnostic accuracy. CIs for sensitivity and specificity are exact Clopper-Pearson CIs. Besides, the performance of the three tests was also estimated by Bayesian Latent Class Models (BLCA) using extensions of the three tests in one population model implemented in a simplified interface application.¹⁵ The BLCA¹⁶ was used to approximate the prevalence and the sensitivities and specificities of all tests. This model does not assume that any test is perfect but considers that each test could be imperfect in diagnosing the true disease status. The true disease status of the patient population was then defined based on overall prevalence (the probability that a patient with suspected SARS-CoV-2 infection is truly infected with SARS-CoV-2). BLCA estimates the prevalence and accuracy of each test based on the observed frequency of the possible combinations of test results.

All the analyses were performed using R software V.4.1.2,¹⁷ including caret R package V.6.0-90,¹⁸ MKmisc R package V.1.8¹⁹ and compare Groups Package v.4.0.¹⁷

RESULTS

Overall, 1186 patients were included in the study. Eight children did not provide the three samples, and four children presented indeterminate RT-PCR results (two for OSS and two for NPS) and were

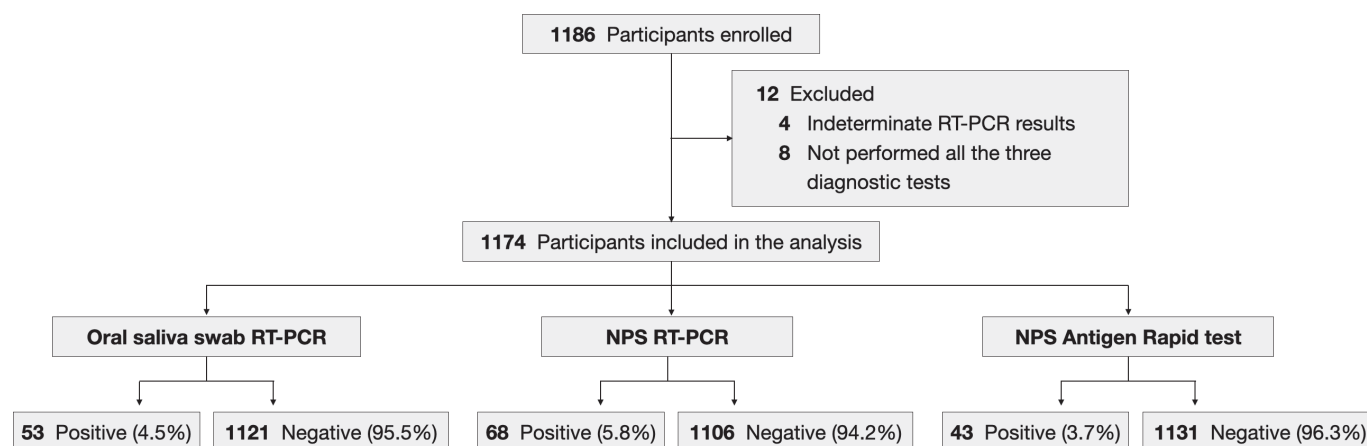


Figure 1 Flow chart of the study and positive results in each of the three evaluated techniques. One NPS antigen rapid test result missing and seven oral saliva swabs collected but not processed due to laboratory workflow problems. NPS, nasopharyngeal swab; RT-PCR, reverse transcription PCR.

Table 1 Clinical characteristics of the children included in the study

	Overall N=1174	Negative n=1101	Positive* n=73	P value†
Sex (male; n, %)	647/1165 (55.1%)	609/1093 (55.7%)	38/72 (52.8%)	0.716
Age (median, IQR)	3.79 (1.67–9.00)	3.68 (1.65–8.65)	8.12 (3.06–12.2)	<0.001
Groups of age				0.001
≤3 years	516 (44.0%)	498 (45.2%)	18 (24.7%)	
>3 years	658 (56.0%)	603 (54.8%)	55 (75.3%)	
Fever				0.429
No	414 (35.3%)	392 (35.6%)	22 (30.1%)	
Yes	760 (64.7%)	709 (64.4%)	51 (69.9%)	
Cough				0.321
No	625 (53.2%)	581 (52.8%)	44 (60.3%)	
Yes	547 (46.6%)	518 (47.0%)	29 (39.7%)	
Unknown	2 (0.17%)	2 (0.18%)	0 (0.00%)	
Sore throat				0.143
No	872 (74.5%)	824 (75.0%)	48 (65.8%)	
Yes	286 (24.4%)	262 (23.9%)	24 (32.9%)	
Unknown	13 (1.11%)	12 (1.09%)	1 (1.37%)	
Runny nose				0.602
No	566 (48.3%)	528 (48.1%)	38 (52.1%)	
Yes	603 (51.5%)	568 (51.7%)	35 (47.9%)	
Unknown	2 (0.17%)	2 (0.18%)	0 (0.00%)	
Wheezing				0.229
No	1071 (91.4%)	1001 (91.1%)	70 (95.9%)	
Yes	101 (8.62%)	98 (8.92%)	3 (4.11%)	
Myalgia				<0.001
No	1042 (88.8%)	987 (89.7%)	55 (75.3%)	
Yes	84 (7.16%)	69 (6.27%)	15 (20.5%)	
Unknown	47 (4.01%)	44 (4.00%)	3 (4.11%)	
Arthralgia				0.064
No	1101 (93.8%)	1036 (94.1%)	65 (89.0%)	
Yes	23 (1.96%)	19 (1.73%)	4 (5.48%)	
Unknown	50 (4.26%)	46 (4.18%)	4 (5.48%)	
Fatigue				0.096
No	1008 (86.0%)	951 (86.5%)	57 (78.1%)	
Yes	139 (11.9%)	125 (11.4%)	14 (19.2%)	
Unknown	25 (2.13%)	23 (2.09%)	2 (2.74%)	
Dyspnoea				0.110
No	1066 (91.4%)	996 (91.0%)	70 (97.2%)	
Yes	100 (8.58%)	98 (8.96%)	2 (2.78%)	
Unknown	8 (0.7%)	7 (0.6%)	1 (1.37%)	
Chest indrawing				0.764
No	1116 (95.9%)	1045 (95.8%)	71 (97.3%)	
Yes	48 (4.12%)	46 (4.22%)	2 (2.74%)	
Unknown	6 (0.51%)	6 (0.55%)	0 (0.00%)	
Headache				<0.001
No	915 (81.1%)	873 (82.4%)	42 (61.8%)	
Yes	213 (18.9%)	187 (17.6%)	26 (38.2%)	
Unknown	45 (3.84%)	40 (3.64%)	5 (6.85%)	
Abdominal pain				0.058
No	879 (77.2%)	818 (76.6%)	61 (87.1%)	
Yes	259 (22.8%)	250 (23.4%)	9 (12.9%)	
Unknown	33 (2.82%)	31 (2.82%)	2 (2.78%)	
Vomiting/nausea				0.012
No	855 (72.9%)	792 (72.0%)	63 (86.3%)	
Yes	318 (27.1%)	308 (28.0%)	10 (13.7%)	
Diarrhoea				<0.001
No	948 (80.8%)	877 (79.7%)	71 (97.3%)	
Yes	225 (19.2%)	223 (20.3%)	2 (2.74%)	
Conjunctivitis				0.622
No	1152 (98.5%)	1079 (98.4%)	73 (100%)	
Yes	18 (1.54%)	18 (1.64%)	0 (0.00%)	
Unknown	2 (0.17%)	2 (0.18%)	0 (0.00%)	

Continued

Table 1 Continued

	Overall N=1174	Negative n=1101	Positive* n=73	P value†
Oral inflammation				0.619
No	1098 (93.6%)	1028 (93.5%)	70 (95.9%)	
Yes	75 (6.39%)	72 (6.55%)	3 (4.11%)	
Rash				0.722
No	1137 (96.9%)	1065 (96.8%)	72 (98.6%)	
Yes	36 (3.07%)	35 (3.18%)	1 (1.37%)	
Alteration taste				0.202
No	917 (97.6%)	856 (97.7%)	61 (95.3%)	
Yes	23 (2.45%)	20 (2.28%)	3 (4.69%)	
Unknown	230 (19.7%)	221 (20.1%)	9 (12.3%)	
Others				0.461
No	1098 (94.1%)	1030 (93.9%)	68 (97.1%)	
Yes	68 (5.83%)	66 (6.02%)	2 (2.86%)	
Unknown	1 (0.09%)	1 (0.09%)	0 (0.00%)	
Days of symptoms (median, IQR)	1.00 (1.00–2.00)	1.00 (1.00–2.00)	1.00 (1.00–2.00)	0.714
Days of fever (median, IQR)	1.00 (0.00–2.00)	1.00 (0.00–2.00)	1.00 (1.00–1.50)	0.464

P values were calculated excluding unknown.

*Positive by any technique.

†P value for the comparison test (continuous, Mann-Whitney U test or categorical χ^2 test).

excluded. Thus, 1174 children were included in the final analysis (figure 1). Median age was 3.8 years (IQR 1.7–9.0), and 516/1174 (44.0%) were ≤ 3 years old. A total of 647/1174 (55.1%) children were males. The median duration of symptoms before emergency department admission was 1.0 days (IQR 1.0–2.0) (table 1).

In total, 73/1174 (6.2%) patients tested positive by at least one of the diagnostic techniques. Out of those 73 patients, 68 tested positive by NPS RT-PCR (93.2%; 5.8% of the total), 53 by OSS RT-PCR (72.6%; 4.5% of the total) and 43 were positive by NPS Ag-RDT (58.9%; 3.7% of the total) (figure 1).

The comparison of OSS RT-PCR and the Ag-RDT in NPS samples versus NPS RT-PCR (gold standard) is shown in table 2. The overall sensitivity was 72.1% (95% CI 59.7% to 81.9%) for OSS RT-PCR and 61.8% (95% CI 49.1% to 73.0%) for the Ag-RDT. The specificity was 99.6% (95% CI 99.0% to 99.9%) for OSS RT-PCR and 99.9% (95% CI 99.4% to 100%) for the Ag-RDT. The kappa index for the OSS RT-PCR and NPS RT-PCR was 0.79 (95% CI 0.72 to 0.88) versus 0.74 (95% CI 0.65 to 0.84) for the Ag-RDT. OSS RT-PCR showed similar performance in children stratified by age. By contrast, the Ag-RDT showed lower sensitivity in children younger than 3 years (table 3).

The estimated medians with 95% credible intervals (CrIs) in the whole cohort and in the BLCA model are shown in table 2. Sensitivity for OSS RT-PCR was 84.8% (95% CrI 71.5%–93.6%) and 72.5% (95% CrI 58.8%–83.6%) for the Ag-RDT. Specificity for OSS RT-PCR was 99.7% (95% CrI 99.2%–99.9%) and 99.9% (95% CrI 99.6%–100%) for the Ag-RDT.

The median Ct values for those patients with positive RT-PCR results were 21.1 (IQR 17.8–30.0) on NPS samples and 32.9 (IQR 28.8–35.6) on OSS samples. The Ct values were higher in OSS than in NPS samples ($Ct(NPS)=0.5 \times (Ct\ saliva)+4.5$, $p=0.027$).

In total, 36/1174 patients (3.1%) tested positive with the three diagnostic tests, 13 cases (1.1%) tested positive only by NPS RT-PCR, 4 cases (0.3%) only by OSS RT-PCR and 1 case (0.1%) only by Ag-RDT (table 4). Ct values for patients with discordant results are shown in online supplemental table S1.

A total of 37 patients had a discordant result in at least one of the three tests (table 3 and online supplemental material). All were invited to provide a blood sample for SARS-CoV-2 serology, and it was available for 22/37 (59.5%) patients.

DISCUSSION

This study evaluates the performance of three SARS-CoV-2 diagnostic tests in a large paediatric population with Covid-19 symptoms showing that the RT-PCR on OSS is a valid diagnostic option in the paediatric population, even better than the widely

used Ag-RDT on NPS. If the turnaround time is sufficiently rapid, OSS RT-PCR would seem to be the better choice for children. The performance of the test improved when NPS RT-PCR was considered as an imperfect gold standard.^{21 22}

NPS is the most widely used sample for SARS-CoV-2 testing, although it is not always well accepted by patients.^{1–3 23} Several studies have shown that different sample types of saliva (dribble pots, suck swabs, oral and oropharynx swabs) are a valid alternative for SARS-CoV-2 testing, but most of the studies included only adults.⁴ To our knowledge, this study is the largest paediatric study comparing OSS with the established gold standard. The results are in concordance with the few studies performed on children.^{5 7 9 10 24} A recent study performed in Dubai with 476 children demonstrated a sensitivity even higher (87.7%) than found here; however, the authors used a saliva sample rather than saliva swabs, and the children were older (mean 10.8 years old).¹⁰ Obtaining direct saliva samples in children younger than 3 years

Table 2 Diagnostic accuracy and agreement of oral saliva swab RT-PCR and rapid antigen test compared with nasopharyngeal swab RT-PCR

Parameters	NPS RT-PCR (assumed as a perfect gold standard (%))*	Bayesian latent class model (%)†
Prevalence	5.8 (4.6–7.3)	5.0 (3.8–6.4)
RT-PCR NPS		
Sensitivity	100	99.3 (92.1–100)
Specificity	100	99.1 (98.3–99.7)
Positive predictive value	100	84.4 (73.3–94.6)
Negative predictive value	100	100 (99.6–100)
RT-PCR oral saliva swab		
Sensitivity	72.1 (59.7–81.0)	84.8 (71.5–93.6)
Specificity	99.6 (99.0–99.9)	99.7 (99.2–99.9)
Positive predictive value	92.5 (80.9–97.6)	92.6 (83.3–98.3)
Negative predictive value	98.3 (97.3–98.9)	99.2 (98.4–99.7)
Antigen rapid test		
Sensitivity	61.8 (49.1–73.0)	72.5 (58.8–83.6)
Specificity	99.9 (99.4–100)	99.9 (99.6–100)
Positive predictive value	97.7 (86.2–99.9)	97.6 (89.9–100)
Negative predictive value	97.7 (96.6–98.5)	98.6 (97.6–99.2)

*Gold standard model assumed that RT-PCR NPS test is perfect (100% sensitivity and 100% specificity; all patients with positive gold standard test are diseased and all patients with negative gold standard test are non-diseased). Values shown are estimated means with 95% CI.

†Bayesian latent class model assumed that all tests evaluated are imperfect. Values shown are estimated median with 95% credible interval.

NPS, nasopharyngeal swab; RT-PCR, reverse transcription PCR.

Table 3 Performance of the studied tests compared with the gold standard test stratified by age

(%, 95% CI)	All N=1174	≤3 years old n=516	>3 years old n=658
RT-PCR on oral saliva swab			
Sensitivity	72.1% (59.8% to 82.27%)	75% (47.6% to 92.73%)	71.1% (56.9% to 82.87%)
Specificity	99.6% (99.1% to 99.9%)	99.6% (98.6% to 99.9%)	99.7% (98.8% to 99.9%)
Positive predictive value	92.4% (82.0% to 97.1%)	85.7% (59.4% to 96.1%)	94.9% (82.1% to 98.7%)
Negative predictive value	98.3% (97.5% to 98.8%)	99.2% (98.1% to 99.7%)	97.6% (96.3% to 98.4%)
Kappa index	0.79 (0.72 to 0.88)	0.79 (0.63 to 0.95)	0.8 (0.71 to 0.89)
Positive likelihood ratio	199.24 (74.1 to 535.9)	187.5 (45.7 to 769.4)	215.6 (53.4 to 869.4)
Negative likelihood ratio	0.28 (0.19 to 0.41)	0.25 (0.11 to 0.59)	0.29 (0.19 to 0.44)
Ag-RT on nasopharyngeal swab			
Sensitivity	61.8% (49.2% to 73.3%)	43.7% (19.8% to 70.1%)	67.3% (52.9% to 79.7%)
Specificity	99.9% (99.5% to 100%)	100% (99.2% to 100%)	99.8% (99.1% to 100%)
Positive predictive value	97.67% (85.4% to 99.7%)	100%	97.2% (83.0% to 99.6%)
Negative predictive value	97.7% (96.9% to 98.3%)	98.2% (97.3% to 98.4%)	97.3% (96.0% to 98.1%)
Kappa index	0.74 (0.65 to 0.84)	0.6 (0.36 to 0.83)	0.78 (0.68 to 0.87)
Positive likelihood ratio	97.7 (85.4 to 99.7)	–	407.9 (57.0 to 2917.6)
Negative likelihood ratio	0.38 (0.3 to 0.5)	0.56 (0.37 to 0.87)	0.33 (0.22 to 0.48)

Ag-RDT, antigen rapid test; RT-PCR, reverse transcription PCR.

of age and children with special needs, who could be at a higher risk of severe Covid-19 (ie, neurological diseases) is challenging. However, unlike direct saliva, oral swabs can be obtained with practically no collaboration from patients. For this reason, we used oral swabs, which is a sample easily feasible and painless for all ages including those children with special needs. We had a high proportion of children younger than 3 years old, which we believe fills the gap of knowledge on the performance of saliva samples at this age. Moreover, analysis by age showed that the accuracy is similar for both groups (≤3 years vs >3 years), unlike the Ag-RDT, which performed poorly in children under 3 years. Children with special needs were not specifically included in this study so the results cannot be directly extrapolated to them.

We found that OSS RT-PCR could detect some cases that were missed by the NPS RT-PCR; four cases were positive for OSS RT-PCR but negative for NPS RT-PCR, as has been described previously.^{7–9} Also, three of those four cases had positive serology but were negative for the Ag-RDT. These data suggest that the positivity on saliva RT-PCR could remain even longer than in NPS RT-PCR, but a SARS-CoV-2 reinfection cannot be fully discarded.

A similar finding was observed in the majority of the 19 cases with a negative result on the OSS but positive on the NPS. Of these 19, 4 had positive serology. An observational study showed that the concordance between paired samples (NPS and saliva) decreased with time, with saliva false negatives increasing in older infections.²⁵ We observed a lower sensitivity of the Ag-RDT in children younger than 3 years old. Moreover, among the four cases with negative Ag-RDT

and positive OSS, three were younger than 3 years. Thus, younger children might benefit from the OSS RT-PCR in testing guidelines possibly before Ag-RDT.

At the time of performing the study, the cost of SARS-CoV-2 Ag-RDT was US\$2–US\$5, which was around 10 times lower than the average price of NPS RT-PCR including the swab and reagents. OSS RT-PCR uses the same diagnostic approach as NPS RT-PCR, but in a different sample, so the cost in our study was the same. Additionally, RT-PCR tests require the prior acquisition of expensive devices to perform the analysis and specialised staff. Considering only the cost, Ag-RDT is a better choice than RT-PCR tests. Furthermore, the turnaround is lower (15 min vs 2–12 hours). However, compared with OSS RT-PCR, it has some disadvantages, such as a lower sensitivity and NPS being a more uncomfortable sample than OSS. So, OSS RT-PCR could be a good alternative to NPS RT-PCR in case of aiming a high sensitivity test and comfortable for patients. Besides, a new approach for SARS-CoV-2 RT-PCR (SalivaDirect) that simplifies RNA extraction has been published.²⁶ In this study, the standard RNA extraction and the SalivaDirect procedure were performed followed by the same RT-PCR with similar results. The potential implementation of the simplified procedure could greatly reduce the cost and the time of the OSS RT-PCR testing, making this method even more attractive.

No systematic or standardised information of the acceptance of the patients, families and operators were collected in this study, but several publications support that OSS is the preferred technique by patients.^{27,28} The acceptability of participating in the study (>99%, data not shown) shows how families acknowledge that finding a more accepted technique to test children is needed. Besides, the collection and processing of samples showed scarce difficulties as only eight children did not provide the three samples, and four children presented indeterminate RT-PCR results.

This study has several limitations. RT-PCR tests and serology were not centralised, which may have introduced some heterogeneity in the results and difficulties in reproducibility. It accounted for only one wave, including the alpha variant as dominant (>70% of isolations), and it may not be fully extrapolated to Omicron or future variants. The possibility of reinfections was not addressed, and not all discordant patients had serology available. Finally, this study included only symptomatic patients (≤5 days of duration), so the results cannot be extrapolated to asymptomatic patients and new studies will be necessary to evaluate this test in SARS-CoV-2 contacts and as a screening test in the general paediatric population. However, as a strength, we evaluate a novel,

Table 4 Detection of SARS-CoV-2 by RT-PCR on NPS or OSS and Ag-RDT in NPS in all 1174 tested children

RT-PCR NPS	RT-PCR OSS	NPS Ag-RDT	Total
Positive	Positive	Positive	36 (3.1%)
Positive	Positive	Negative	13 (1.1%)
Positive	Negative	Negative	13 (1.1%)
Positive	Negative	Positive	6 (0.5%)
Negative	Positive	Negative	4 (0.3)
Negative	Negative	Positive	1 (0.1%)
Negative	Positive	Positive	0 (0.0%)
Negative	Negative	Negative	1101 (93.8%)

Ag-RDT, antigen rapid test; NPS, nasopharyngeal swab; OSS, oral saliva swab; RT-PCR, reverse transcription PCR.

comfortable and easy-to-collect sample in children, which has not been previously thoroughly evaluated in the paediatric population, mainly in the younger children.

In conclusion, OSS RT-PCR seems a more suitable and friendly technique for younger patients who must be tested very frequently and might help to maximise the number of patients tested, playing an important role in the control of the disease.

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Sabe quando é que o inalador está vazio?

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RESUMO

Contexto A revisão da medicação está recomendada nas consultas de asma. A presença de propulsor nos inaladores de dose calibrada (IDC) torna difícil identificar quando o inalador está vazio. A pandemia da COVID-19 resultou num movimento no sentido de uma monitorização mais virtual dos cuidados de saúde. O nosso objetivo foi avaliar se os pacientes identificam quando o inalador está vazio e o método de eliminação do inalador.

Métodos Projeto de melhoria de qualidade prospetivo e multicêntrico. Dados recolhidos de crianças com asma e outras doenças respiratórias.

Medidas de resultados Foi perguntado às crianças/cuidadores que frequentavam o hospital como identificavam um inalador de salbutamol vazio; foram revistos os contadores de dose nos inaladores de prevenção e as práticas de eliminação.

Resultados 157 pacientes selecionados. 125 (73,5%) pacientes consideraram um inalador vazio como estando ou cheio/parcialmente cheio. 12 de 66 (18,2%) inaladores de prevenção com um contador de dose encontravam-se vazios. 83% descartaram os seus inaladores em caixote do lixo.

Conclusões Os pacientes não conseguem identificar de forma fiável quando o seu IDC está vazio. Verifica-se uma necessidade urgente de melhorar a tecnologia dos inaladores e de fornecer orientações adequadas sobre como identificar quando um IDC está vazio.

BACKGROUND

Asthma-related morbidity and mortality in children remain high in the UK.¹ The national guidelines for management of asthma,² quality standards, resources focusing on adherence, inhaler technique and asthma plans, annual asthma reviews and post-attack follow-up advice³ have not resulted in sustained reduction in asthma attacks in children.^{4,5}

The National Institute for Health and Care Excellence (NICE) quality standards (2018)⁶ recommend medication review at every asthma appointment. Metered dose inhalers (MDIs), due to their reliability and ease of delivery of medications, have been commonly used in the treatment of paediatric and adult asthma for more than six decades. The crucial disadvantage of the MDIs is the inability to identify the amount of medications left in the inhalers. This is due to the design of MDIs which contain a propellant along with the active drug to expel the labelled number of actuations. Studies have shown that up to 86 actuations can be done just with the inhaler propellant after all the medications have been used up.⁷ The amount of the active drug in these additional actuations can be negligible despite the appearance of a visible 'spray' of propellant. Manufacturers have incorporated dose counters into some brands of the inhaler devices, to enable patients to identify the number of remaining actuations. However, not all inhalers have a dose counter—including salbutamol (Ventolin, Salamol) in the UK.

Salbutamol inhaler is an essential emergency medication in the management of young people with asthma and is also prescribed in non-asthmatic

What is already known on this topic?

- ▶ Asthma is one of the most common chronic diseases in children.
- ▶ The COVID-19 pandemic has resulted in more virtual medical reviews.
- ▶ Medication reviews are recommended during clinic appointments.

What this study adds?

- ▶ Children and families are unable to identify when their salbutamol metered dose inhalers (MDIs) are empty.
- ▶ There is no consistent information available in national asthma guidelines and medication information leaflets in identifying when the inhalers are empty.
- ▶ One-fifth of preventer inhalers with the dose counters were empty.

How this study might affect research, practice or policy

- ▶ The pharmaceutical industry and the national guidelines should produce educational information regarding identification of empty inhalers and improve inhaler technology.
- ▶ Along with the use of a right spacer and good inhaler technique, identification of an empty MDI should be part of essential asthma care.
- ▶ Dose counters should be mandated in all inhalers.

respiratory conditions. The absence of a dose counter presents the risk of patients and their families continuing to use the inhaler even though there is no remaining active drug element remaining in the canister.⁸ The manufacturer recommends remembering the date when the new inhaler was opened, and manually counting the total doses used as the only reliable method to identify an empty inhaler. Shaking the inhaler, observing actuation 'spray' and floating the canister in a bowl of water are described but not recommended.⁹

Corticosteroid inhalers containing beclomethasone (Clenil Modulite) and fluticasone (Flixotide) are commonly prescribed in children but not all have dose counters. Other inhalers like Seretide (fluticasone/salmeterol) and Symbicort (budesonide/formoterol) do have dose counters.

The COVID-19 pandemic has resulted in significant increase in remote consultations and monitoring resulting in new challenges in maintaining

essential asthma care. As part of a quality improvement project, we prospectively evaluated the knowledge of children and families in identifying the amount of medications left in their inhalers. We also reviewed disposal of inhalers, the information available on the National Health Service (NHS) website,¹⁰ British Thoracic Society/Scottish Intercollegiate Guidelines Network (SIGN²) and NICE guidelines¹¹ for asthma management and the drug information leaflets of the commonly used inhalers.

METHODS

This project was conducted at seven acute hospitals which are part of the West Midlands Paediatric Severe Asthma Network.¹² Prospective cross-sectional data were collected for children attending routine outpatient appointments and those admitted to the hospital. The quality improvement project was registered with each centre's audit and clinical governance department. As part of routine care, patients were encouraged to bring their medications to the clinic or during hospital admissions.

Children with asthma and preschool wheeze (PSW) as well as children with bronchiectasis and cystic fibrosis who were prescribed inhalers were included. Children were assessed by a trained paediatric respiratory nurse and/or by a senior clinician. Anonymised demographic data on age, sex, diagnosis, asthma attacks (where applicable), inhaler technique and method of inhaler disposal were analysed. Data were entered from each centre into an online proforma (Microsoft Forms).

1. Children/families were shown an MDI salbutamol inhaler which was already actuated the recommended 200 doses (empty inhaler) and asked how do they know that the inhaler had medicines left in them.
2. The children and families who brought the preventer inhaler, which had a dose counter, were checked for the number of actuations left by reading the number on the dose counter. These inhaler brands included Seretide 50, 125, 250, Symbicort MDI and DPI, Clenil Modulite (only those with dose counters) and Relvar.
3. The information leaflets enclosed with each of the commonly used inhalers were reviewed for details regarding how to use the inhaler, information regarding inhaler technique and how to identify an empty inhaler.

RESULTS

Data were collected from 157 children between October 2020 and September 2021. One hundred and seven (68.1%) were boys, the median age was 9.5 years (IQR 2–15). One hundred and eighteen children (75.2%) had asthma, 19 (12.1%) PSW, 5 (3.2%) cystic fibrosis and 15 (9.5%) bronchiectasis. In children with asthma or PSW (n=137), median asthma or wheeze attacks requiring emergency department visits within the last 12 months were 2 (IQR 0–10), and high dependency unit admissions were 0.5 (IQR 0–4) (table 1).

Eighty-six (54.8%) said they were able to identify an empty inhaler correctly and 71 (45.2%) were unsure/not aware. However, 105 (69.9%) sought to identify medication left in the inhaler by shaking it and 27 (29.9%) looked for visible aerosol during actuation, both of which are incorrect. Only three patients said that they will look at the dose counter and two actually kept count of actuations delivered.

Inhaler technique and spacer device check

Inhaler technique was checked in 152 of 157 patients (96.8%) and was found to be satisfactory in 127 of 152 (83.5%). One hundred thirty-eight of 157 brought a spacer device to the clinic and 127 of 138 (92%) were using an appropriate spacer for age.

Identification of medicines remaining in inhaler by visual method

One hundred and twenty-three children and families were shown a salbutamol inhaler that had been actuated 200 times (empty inhaler). Ninety (73.5%) said the inhaler was either full or partially full and 33 (26.5%) said the inhaler was empty.

Table 1 Characteristics of children opportunistically enrolled in the project

n	157
Male (n, %)	107 (68.1)
Age	9.5 years (2–15 years)
Diagnosis (n, %)	
Asthma	118 (75.2)
PSW	19 (12.1)
CF	5 (3.2)
Bronchiectasis	15 (9.5)
Asthma/wheeze attacks (n=137)	
ED (median, IQR)	2 (0–3)
HDU (median, IQR)	0.5 (0–2)
Inhaler technique checked (n)	152/157 (96.8%)
Satisfactory	127/152 (83.5%)
Suboptimal	25/152 (16.5%)
Spacer device checked (n)	138/157 (87.9%)
Right spacer	127/138 (92%)
Wrong spacer	11/138 (8%)

Data shown as number of patients (n), percentage (%) and median (range).

CF, cystic fibrosis; ED, emergency department; HDU, high dependency unit; PSW, preschool wheeze.

Review of preventer inhalers with the dose counter

Sixty-six patients (42%) had a preventer inhaler with a dose counter with them during clinic consultation or hospital admission. In 12 of 66 (18.2%) of the patients, the dose counter read 0.

Review of the patient information leaflets enclosed with the inhalers

Neither the Salamol or Ventolin information leaflets contained any information on how to identify when 200 actuations had been performed. Symbicort and Clenil brands with dose counters had information on when to change the inhaler by looking at the number on the dose counter. Seretide and Clenil (without the dose counter) did not have any information regarding when to change the inhaler.

Inhaler disposal

One hundred and thirty-three (84.7%) patients and families were asked how they disposed of their inhalers. One hundred and eleven (83%) disposed of them in general household waste, 12 (9%) returned them to the pharmacy and 10 (8%) disposed of them in recycle bins.

DISCUSSION

Although medication review is recommended at medical reviews, there was no information available on the NHS website or in the UK national asthma guidelines regarding identification of an empty MDI. This is a crucial area requiring improvement in the provision of asthma education. The risk presented by an unidentified empty inhaler might be addressed by a system of recording administered doses or the incorporation of a dose counter into all MDIs. It is to be noted that except for counting the actuations, there is no easy way of identifying when the medicine has run out in an MDI without a dose counter. Worryingly, we report that three-quarters of patients and families were unable to identify an empty MDI. One-fifth of accompanying preventer inhalers with dose counters were empty, highlighting the need for improvement in the information provided to the patients and families during medication reviews. Intriguingly, more than 80% of children had a good inhaler technique and were carrying an appropriate spacer device including the 12 children who were carrying the empty preventer inhaler. This clearly emphasises the need for including identifying an empty MDI as part of essential care of children who are prescribed the inhalers.

The information leaflet enclosed in the box of the most commonly used MDI, salbutamol, does not provide any information on how to identify doses left in the inhaler. Moreover, the leaflet contains pictures showing wrong inhaler technique, that is, administering salbutamol without the spacer device, which is not recommended in children.

The face-to-face appointments should include reviewing the inhaler technique and where applicable, show them the inhaler dose counter. If the inhalers do not have the dose counter, the patients/carers should be advised to count the number of actuations. The text or telephone appointment reminders should contain information encouraging families to bring the inhalers to the clinic. For children who are admitted to the hospital with wheeze/asthma attacks or other respiratory conditions who are prescribed inhalers, the medications should be checked before discharge.

Virtual appointments, where applicable, should always be using a video platform where the inhalers can be checked. Telephone appointments should be discouraged. It is important for the patients and carers to be educated when a new inhaler is prescribed. They need to be shown the features of the inhaler along with checking the technique. Patients should also be signposted to the online resources on inhalers available on the Asthma UK/beat asthma websites.^{13 14}

The majority of patients disposed of their inhalers in general waste. The NHS is working to reduce its carbon footprint to net zero by 2040. Medicines account for 25% of emissions within the NHS with inhalers making up 3%.¹⁵ The inhalers should be returned to the pharmacy for safe disposal and should not be put in waste bins.

The limitations of the data include cross-sectional, descriptive observational design and data collection. Detailed data on the duration of symptoms or medications were not collected as the primary aim of the study was to identify if children and parents were able to identify when their inhalers were empty as part of their medication review. We included only patients who had face-to-face appointments and those who brought their inhalers to the appointments.

What do the study results mean?

Our findings raise the important patient safety issue of children being potentially unable to access an effective (not empty) salbutamol inhaler during an acute asthma attack. It also has implications on medication reviews and service delivery in the COVID-19 pandemic era where more virtual appointments are encouraged. There is an urgent need for health regulators to work with the pharmaceutical industry to improve the inhaler technology and provide the right, vital information to patients using MDIs. In Australia, since August 2020, all salbutamol inhalers have a dose counter.¹⁶ The asthma guidelines should explicitly provide

information to patients and healthcare providers on how to identify when their inhaler is empty. Along with inhaler technique and emphasis on asthma plans, identification of when the inhalers are empty should be part of the standard asthma management and educational package delivered to patients. Disappointingly, there have been minimal advances in technology used in commonly prescribed inhalers in the last 60 years.

There is also an urgent need for dose counters to be made available with all salbutamol and preventer inhalers. Although adults with respiratory diseases including asthma and chronic obstructive lung disease account for majority of the MDIs dispensed in the UK, there is very little information available on identifying the empty inhaler.

Finally, healthcare professionals must all take responsibility for raising awareness of the safe and environmentally friendly disposal of MDIs.

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ARTIGO ORIGINAL

Altura e conteúdo mineral ósseo após uso de corticosteroides inalados nos primeiros 6 anos de vida

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RESUMO

Contexto Os bebês e crianças jovens podem ser particularmente suscetíveis aos potenciais efeitos secundários de corticosteroides inalados (CEI) na altura e no conteúdo mineral ósseo (CMO), mas este aspeto tem sido raramente estudado em estudos prospetivos de longo prazo.

Métodos Foram incluídas crianças de duas coortes de Estudos Prospetivos sobre a Asma na Infância de Copenhaga. O uso de CEI foi registado prospectivamente desde o nascimento até aos 6 anos de idade e foi calculada a dose cumulativa. Os resultados primários foram a altura e o CMO a partir de exames de absorciometria de raios X de dupla energia (DXA) aos 6 anos de idade.

Resultados Aos 6 anos, um total de 930 crianças (84%) das coortes apresentaram uma medida de altura válida e 792 (71%) apresentaram um exame DXA. 291 crianças (31%) receberam uma dose acumulada de CEI equivalente ou superior a 10 semanas de tratamento padrão antes dos 6 anos de idade. Encontrámos uma associação inversa entre o uso de CEI e a altura, $-0,26$ cm (95% IC: $-0,45$ a $-0,07$) por cada 1 ano de tratamento padrão entre os 0 e 6 anos de idade, $p=0,006$. Este efeito foi induzido principalmente por crianças com tratamento continuado entre os 5 e 6 anos de idade ($-0,31$ cm (95% IC: $-0,52$ a $-0,1$), $p=0,004$), embora não se tenha verificado uma associação significativa em crianças que interromperam o tratamento pelo menos 1 ano antes dos 6 anos de idade ($-0,09$ cm (95% IC: $-0,46$ a $0,28$), $p=0,64$). Não se verificou qualquer associação entre o uso de CEI e o CMO aos 6 anos de idade.

Conclusões O uso de CEI na primeira infância foi associado à redução da altura aos 6 anos de idade, mas apenas em crianças com tratamento continuado no sexto ano de vida

INTRODUCTION

Treatment with inhaled corticosteroids (ICS) is the preferred controller therapy for the management of asthma in children, but has potential side effects.^{1,2} In particular, concerns about a decreased linear growth and bone mineralisation have been raised.^{2,3} The risk of growth suppression by ICS might be especially relevant in infants and younger children, ages 1–6 years, due to the high growth velocity in this age group.⁴ These children may also be at greater risk for adverse systemic effects due to the relatively higher prescribed doses of ICS per body weight compared with older children,^{5,6} although this is uncertain from pharmacokinetic studies.^{7,8}

The negative, short-term effect of ICS treatment on height and growth velocity in the first year of treatment is well studied; it shows around a 1 cm decrement in linear growth velocity,^{2,9,10} but evidence on the effects of long-term treatment, over a period of several years, is sparse, particularly in young children.¹¹ Randomised controlled trials (RCTs) are generally not conducted over long periods of time (ie, more than 2 years)^{12–14} and only a few observational studies have followed children over several years.¹⁵ The results of these studies are

Key messages

What is the key question?

► Does the use of inhaled corticosteroid 0–6 years of age result in reduced height or bone mineral content at age 6 years?

What is the bottom line?

► Treatment with inhaled corticosteroid has limited adverse effects on height and bone mineral content, also in the youngest group of children 0–6 years of age. The height development of a subgroup of children with continued treatment and the largest cumulative doses should be explored.

Why read on?

► To our knowledge, this is the first study evaluating height and bone mineral content side effects from inhaled corticosteroid use prospectively during the first 6 years of life. The study is of interest to clinicians when balancing risk and benefits from inhaled corticosteroids in the young children and when informing parents about potential side effects.

conflicting. Some studies suggest negative, long-term effects of ICS treatment during 1 year or more on height,^{16–18} while others do not.^{12,15,19,20} One long-term RCT (the PEAK-study), of 2 years ICS treatment in preschool age, followed the children for 2 years after treatment cessation and suggested a reduced linear growth, but only in a subgroup of children of lesser weight.^{6,16}

We aimed to investigate the effect of ICS treatment in the first 6 years of life on height and bone mineral content (BMC) at age 6 years in the two Copenhagen Prospective Studies on Asthma in Childhood birth cohorts (COPSAC₂₀₀₀ and COPSAC₂₀₁₀) where use of all ICS was registered prospectively from birth.^{21,22} This is the first study evaluating the use of ICS prospectively during the first 6 years of life in a mother–child cohort setting with controlled diagnosis and treatment according to predefined algorithms.

METHODS

Study population

COPSAC₂₀₀₀ is a high-risk mother–child cohort study of 411 children born to mothers with a history of asthma, followed at the COPSAC clinical research unit from the age of 1 month. COPSAC₂₀₁₀ is a population-based mother–child cohort study of 700 children, who were followed since week 24 of gestation. Details of the cohorts, baseline characteristics and recruitment processes are described in the online supplemental methods and cohort design papers.^{21,22}

Inclusion criteria for the present study were height measurements at age 6 years and dual-energy X-ray absorptiometry (DXA) scan at ages 6–7 years, data on relevant confounders and prospectively registered use of ICS.

Standardised treatment with corticosteroids

All children were followed at the COPSAC research unit for scheduled clinical visits and acute care visits whenever parents felt there was a need for medical attention. Daily diary records were used to monitor lung symptoms and use of ICS. The diary records were reviewed by the COPSAC paediatricians together with the families. Standard dosage of ICS in COPSAC₂₀₀₀ was budesonide (BUD) 400 mcg daily by metered-dose inhaler (MDI) and a spacer and in COPSAC₂₀₁₀ fluticasone propionate (FP) 200 mcg daily by MDI and a spacer.²⁰¹⁰ Definition of symptoms and the treatment algorithms are described in more detailed in the online supplemental methods and the cohort design papers.^{22 23}

Nested interventional study: prevention of asthma in childhood study

All of the COPSAC₂₀₀₀ children were randomly assigned to receive either inhaled BUD 400 µg daily or placebo for 14 days following any episode of three consecutive days of asthma-like symptoms in the first 3 years of life until fulfilling the criteria for regular treatment.²⁴

Assessment of corticosteroid exposure

At every visit the child's use of medication, as prescribed, was verified with the families, validated in the national online platform for prescribed medicine by all health professionals and registered online in the COPSAC database. If on the rare occasion the child had been prescribed ICS from physicians outside COPSAC, this was recorded and included in the present study. Corticosteroids administered during hospitalisation were registered through review of the patient records.

The cumulative dose of corticosteroids (inhaled, intranasal and oral) for each child was calculated as the prescribed daily dose in mcg multiplied by the registered treatment duration. ICS registered as administrated, less than 3 days was considered not reliably registered and was not included in the study. The cumulative dose of standard ICS treatment (inhaled and intranasal) was used as primary exposure. The different potencies of corticosteroids were made equivalent and calculated as BUD equivalents, by multiplying FP doses by 2 and dividing prednisolone doses by 10.^{25–27}

ICS usage was furthermore categorised in four groups. The reference group included children with no use or a cumulative ICS dosage less than or equal to 10 weeks of treatment with standard ICS dosage (400 mcg BUD daily or equivalent). This was to avoid inclusion of children with a low cumulative exposure, who were considered unlikely to have any clinical side effects. Three months was the shortest period of regular treatment according to the treatment algorithm, see the online supplemental methods. The remaining children were divided into tertiles of increasing ICS exposure: group 1: 30 400–94 000 mcg, group 2: 100 000–262 400 mcg, group 3: 265 200–983 250 mcg. In a sensitivity analysis, the cumulative ICS dose was also calculated per kilogram of bodyweight using the yearly bodyweight measurements.

Stratified analyses were performed according to current versus no ICS use in the sixth year of life. Current users were defined as those still treated between ages 5 and 6 years, while previous users had stopped treatment at age 5 as the latest.

Anthropometrics

Length/height was measured regularly at the COPSAC clinical research unit. Length was measured until age 2 years using the infantometer, Kiddimeter (Raven Equipment, Essex, England). Height was measured in children after age 2 years and in parents by a Harpenden stadiometer (Holtain, Crymych, Dyfed, Wales),^{12 22} which was calibrated yearly.

We used height at age 6 years as primary outcome. Height at age 3 was analysed as a sub-analysis.

DXA scans

Whole body DXA scans²⁸ were performed with Lunar iDXA densitometer (GE-Healthcare, Fairfield, Connecticut, USA) and analysed with enCore software (GE-Healthcare). Thereafter, an experienced specialist validated the images. The DXA scan provided measures of bone composition, BMC (g hydroxyapatite) and bone mineral density (BMD) (g/cm²), and the region of primary interest was total body less head.^{29 30} It has been argued that BMD is not a reliable marker of bone mineral accrual in children; therefore, we chose BMC as primary DXA outcome.^{31–33} BMC measurements were calibrated for age, projected bone area, height and weight at scanning day, termed size-adjusted BMC.³¹ DXA scans from age 7 years in COPSAC₂₀₀₀ and from age 6 years in COPSAC₂₀₁₀ were used.

Covariates

Covariates included child's race (Caucasian yes/no), sex (male/female), season of birth (fall, spring, summer, winter), birth length (cm) and weight (kg), gestational age (days), birth weight for gestational age (Marsal-percentage),³⁴ exclusive breastfeeding duration (days), asthmatic mother (yes or no), maternal smoking during third trimester (yes or no), mother's and father's height (cm), social circumstances (score) and baseline height (z-score).

The Marsal percentage is the birth weight for gestational age z-score units and was used as a covariate in the analyses as an estimate of intrauterine growth. The Marsal percentage should be a better measurement than birth weight of fetal growth in the preterm period and therefore used instead of birth weight in the analysis.

For the children treated with ICS, the baseline length/height was the z-score length/height closest to visit 1 year, but before starting treatment (above 14 days of ICS). For non-treated children 0–6 years of age (ie, controls), the z-score length age 1 year was used. The z-score length/height was chosen as baseline height instead of birth length, because the measurement of length at birth is prone to inaccuracy and less strongly associated with height in later life than is length/height at or after 1 year of age.³⁵

Severe asthma exacerbations in the first 6 years of life were used as a measure of asthma severity and defined from acute hospitalisation or acute need of oral corticosteroids and/or course of high dose ICS.

Statistical analyses

Pooled analysis of both cohorts was performed using multiple linear regression models including cohort as covariate. As sensitivity analyses, we also performed fixed and random-effects meta-analyses. The primary analysis was based on the cumulative ICS dose as a continuous measure. Analyses of categories of ICS exposure were performed secondarily for descriptive purposes.

Effect estimates were calculated per 1 year of standard ICS treatment (by dividing the cumulative dose of standard ICS in mcg with

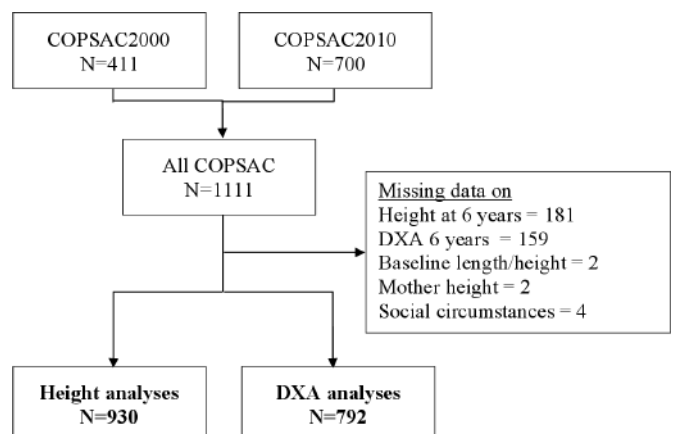


Figure 1 Flowchart of the study population. COPSAC, COpenhagen Prospective Studies on Asthma in Childhood; DXA, dual-energy X-ray absorptiometry.

Table 1 Height at age 6 by inhaled corticosteroid 0–6 years, all, male and female. ICS-treated children are stratified by current treatment: that is, 'no current use' excludes children with any ICS in 6th life year. Effects are by 1 year standard treatment

	All children			No current ICS*			Current ICS*		
	n	Adjusted estimate† (95% CI)	P value	n	Adjusted estimate† (95% CI)	P value	n	Adjusted estimate† (95% CI)	P value
All	930	−0.26 (−0.45 to −0.07)	0.006	819	−0.09 (−0.46 to 0.28)	0.64	658	−0.31 (−0.52 to −0.1)	0.004
Males	466	−0.23 (−0.48 to 0.01)	0.06	402	−0.18 (−0.66 to 0.30)	0.46	318	−0.30 (−0.57 to −0.02)	0.03
Females	464	−0.31 (−0.61 to −0.008)	0.04	417	−0.0003 (−0.59 to 0.59)	1.0	340	−0.34 (−0.69 to −0.003)	0.05

Number of children having received no ICS 0–6 years of age: n=547 (ie, controls).

*Current ICS use=ICS received in age 5–6 years.

†Adjusted for: age at visit 6 years, sex, cohort, social circumstances*cohort, mother height, mother smoking third trimester, gestational age, Marsal-percentage and baseline length/height (definition in manuscript).

ICS, inhaled corticosteroids.

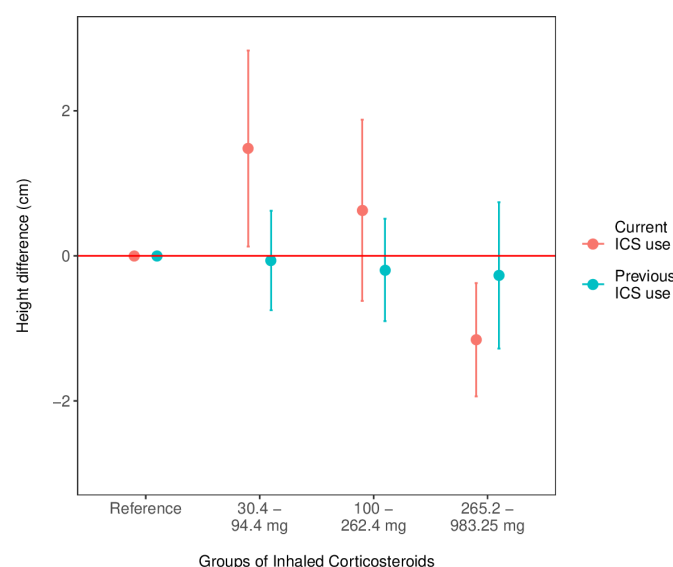
146000 which is equivalent of 1 year/365 days treatment with BUD 400 mcg per year) and presented with 95% CIs. A p value <0.05 was used as level of significance. Missing data were treated as missing observations. Only children with complete data on selected covariates were included in the analyses. Statistical analyses were performed with R V.3.4.0 (R Foundation for Statistical Computing, Vienna, Austria).³⁶

Analyses based on tertiles of ICS exposure were performed as secondary analyses for descriptive purposes.

Covariates associated with both ICS exposure and outcomes (p<0.1) were considered true potential confounders and were selected based on univariate analyses. χ^2 test was used for categorical variables and two-group analysis of variance, equivalent of a t-test, was used for continuous variables. In addition, we a priori selected maternal height as covariate in the model, as a measure of genetic height and the same was the case for maternal smoking during third trimester and social circumstances which were selected because of a known association with both exposure and outcome.^{37–40} Due to many missing values for paternal height, this was adjusted for a sensitivity analysis only.

The final height analysis models were confounder adjusted for age, sex, cohort, social circumstances, mother's height, mother's smoking in third trimester, gestational age, Marsal-percentage and baseline length/height. The BMC analyses final model was confounder adjusted for cohort and mother's smoking third trimester. Prior to analysis BMC was adjusted for age, sex, bone area, height and weight at DXA scan—termed size-adjusted BMC. Adjusting for social circumstances was performed as an interaction term to consider the difference in the principal component analysis score in the two COPSAC cohorts.

We performed several sensitivity analyses: the primary analyses were performed for the two cohorts separately, and with the cumulative exposure calculated in relation to yearly body weight.

**Figure 2** Height at age 6 years by ICS exposure, stratified by current or previous ICS use. ICS, inhaled corticosteroid.

The primary analysis was additionally adjusted for father's height, asthma exacerbations and child body mass index (BMI) at age 6 years. Stratified and interaction analyses were performed for sex and weight at age 1 year. In the analysis stratified on weight at the 1 year visit we used weight z-scores accounting for sex and age. This corresponded to an absolute weight cut-off of approximately 9.5 kg for girls and 10 kg for boys.

As a supplementary analysis, we stratified the main analysis by the single nucleotide polymorphism (SNP) rs591118 because this genetic variation in the PDGFD gene locus has been shown to modify the risk of systemic adverse effects to ICS in terms of adrenal suppression in children with asthma.⁴¹ This was coded as a continuous variable counting number of alleles increasing susceptibility to corticoid-induced adrenal suppression.

A power-calculation based on 930 children to determine the detectable effect size was performed. With an SD on height at age 6 years of 5.0 cm,⁴² the study had a power of 80% for the detection of a mean difference in height down to 1.21 cm between 30% children with versus 70% children without exposure to corticosteroid (ie, the reference group with less than or equal to 10 weeks of treatment with standard ICS dose), significance level p=0.05.

RESULTS

Baseline

Of the 1111 children in the two cohorts, 930 (84%) had height measurement at 6 years (mean age, 6.01 years; SD 0.15) and 792 (71%) had a DXA scan (6.40 years; SD 0.34) (figure 1). Among the 930 included children, differences between baseline characteristics are shown in online supplemental table S1.

Univariate analyses were performed to select covariates associated with both ICS exposure and outcome. The results of these analyses, online supplemental table S2, show that gestational age, Marsal%, length and weight at birth were considered to be true potential confounders.

Of the 930 children with age 6 height data, 291 children (31%) had received a cumulative ICS dose equivalent to or above 10 weeks of standard treatment (online supplemental table S3). The median (IQR) cumulative dose of treatment with ICS among ever treated was 101 600 mcg (233 073 mcg) corresponding to 0.7 (1.6) years of standard treatment.

Cumulative doses in the four ICS stratified exposure groups are shown in online supplemental table S3. The children in the group with highest exposure received ICS corresponding to a median (IQR) of 2.9 (1.6) years of standard treatment.

The number of children with no current ICS treatment between age 5 and 6 and current treatment between age 5 and 6 was respectively n=272 and n=111.

ICS exposure and height

The cumulative ICS dose as a continuous measure from 0 to 6 years was inversely associated with age 6 years height; confounder adjusted estimate: −0.26 cm (95% CI: −0.45 to −0.07) per year standard treatment, p=0.006 (table 1).

Stratifying by current ICS use in the sixth year of life showed that the children still treated after age 5 had a −0.31 cm height

Table 2 Mean difference in height age 6 years in groups of increasing ICS exposure. Results are shown for all children and separately for children with current and previous use of ICS. previous steroid users had not received ICS between age 5 and 6 while current steroid users had received ICS age 5–6

All children, n=930					
	All	Group 0	Group 1	Group 2	Group 3
n	930	639	97	97	97
Group versus group 0 (95% CI)		Reference	0.24 (–0.39 to 0.87)	–0.02 (–0.65 to 0.61)	–0.86 (–1.49 to –0.22)
P value			0.45	0.95	0.008
Current users of ICS, n=111					
n	658	554	19	22	63
Group versus group 0 (95% CI)		Reference	1.48 (0.13 to 2.83)	0.63 (–0.62 to 1.88)	–1.16 (–1.94 to –0.38)
P value			0.032	0.32	0.004
Previous users of ICS, n=272					
n	819	632	78	75	34
Group versus group 0 (95% CI)		Reference	–0.06 (–0.75 to 0.62)	–0.19 (–0.90 to 0.51)	–0.27 (–1.28 to 0.74)
P value			0.85	0.59	0.60

The reference group (0) include standard treatment from 0 to a cumulative maximum of 10 weeks treatment with a standard dose. The cumulative ICS dose in the other treatment groups was based on tertiles of steroid exposure in all treated children.

Means have been adjusted for: age at visit 6 years, sex, cohort, social circumstances*cohort, mother height, mother smoking third trimester, gestational age, Marsal-percentage and baseline length/height.

ICS, inhaled corticosteroids.

difference per year standard treatment (95% CI: –0.52 to –0.1), $p=0.004$, whereas there was no significant association for children not treated after age 5; –0.09 cm height difference per year ICS treatment (95% CI: –0.46 to 0.28), $p=0.64$ (table 1).

Analyses of ICS exposure in stratified groups showed a decreasing height by increasing ICS exposure only for the children with current use of ICS in their sixth year of life, and only for the children in the high exposure group (figure 2). For current users in the highest ICS exposure group, the mean height was 1.16 cm lower (95% CI: –1.94 to –0.38), $p=0.004$ compared with the group with no/low dose (table 2).

Children with low-dose current use had increased height relative to the group with no/low dose, but this was also the stratum with lowest numbers ($n=19$) and the p value was only borderline significant ($p=0.032$).

Analysing ICS dose from 0 to 3 years of age in relation to height at age 3 also showed a significant inverse association (–0.53 cm per year of ICS treatment (–0.77 to –0.28), $p<0.0001$, $n=880$).

Sensitivity analyses

Including all corticosteroids (inhaled, intranasal and oral) did not change the overall results in relation to ICS exposure and 6-year height (–0.25 cm (95% CI: –0.42 to –0.07), $p=0.0006$). To consider that children with different body size might receive a relatively higher dose, we also performed an analysis where the cumulative exposure was calculated in relation to yearly body weight, showing similar results (online supplemental table S4).

Results were also similar after adjustment for 6-year BMI (–0.32 cm (95% CI: –0.51 to –0.14), $p=0.0007$) and asthma exacerbations (–0.33 cm (95% CI: –0.56 to –0.11), $p=0.004$) and when analysing the two cohorts separately and in fixed versus random-effect meta-analyses (online supplemental figure S1). Additionally,

adjusting the main result for father's height did not change the overall result (data not shown).

Sex-stratified analyses indicated no sex-specific effects (table 1) and no significant interaction with sex was found ($p=0.67$). There was a tendency of stronger association seen in children with weight below mean at 1 year (–0.40 cm (95% CI: –0.70 to –0.10), $p=0.01$ versus –0.26 cm (95% CI: –0.51 to –0.02), $p=0.04$) but this difference was not statistically significant (interaction $p=0.17$).

ICS exposure and BMC

There was no association between cumulative ICS exposure analysed as a continuous measure and 6-year size-adjusted BMC (–0.01 g (95% CI: –2.24 to 2.23) per 1 year ICS treatment, $p=0.99$ (table 3), nor any significant associations in the analyses stratifying ICS exposure in groups (online supplemental table S5). Similarly, there was no significant association in sex-stratified analyses (table 3) and no significant interaction with sex (data not shown).

ICS exposure and genetic risk

There was no significant interaction between rs591118 genotype and ICS exposure on 6-year height ($p=0.11$), and genotype stratified analyses suggested a trend in the opposite direction than expected with a stronger association in children with no risk alleles than in children with 1 or 2 risk alleles (online supplemental table S6).

DISCUSSION

Primary findings

We found a significant inverse association between ICS exposure during the first 6 years of life and height by age 6, but only in children with current ICS use in the sixth year of life. There was no association between ICS exposure during the first 6 years of life and bone health by age 6.

Strengths and limitations

The primary strength of this study is the daily longitudinal recording of all prescribed medicine and meticulous registration of potential confounders. The children were diagnosed and treated at a single clinical research facility according to standardised procedures and predefined algorithms,^{21 22 24} and compliance of medicine was evaluated from the national platform for all prescribed medicine every 6 months. In both cohorts, the standard ICS, in standard dosages, was administered by identical devices. Furthermore, we were able to combine data on both height and BMC as endpoints in two independent but methodologically comparable cohorts, yielding similar results.

This is the first study evaluating the use of ICS and potential impact on height and BMC at this young age and with 6 years of prospective monitoring of medication use.

Table 3 Associations between cumulative standard doses of inhaled corticosteroids and bone mineral content (total body less head) at age 6 years comparing children treated and not treated. Estimates are per year of standard treatment with ICS

ICS 0–6 years of age and BMC (g) at age 6	Number of children	Difference in BMC, estimate (95% CI)*	P value
All	792	–0.01 (–2.240 to 2.225)	0.995
Males	394	1.13 (–1.999 to 4.258)	0.478
Females	398	–1.69 (–4.91 to 1.53)	0.303

*Prior to analysis BMC was adjusted for age, (sex), bone area, height and weight at DXA scan and termed size-adjusted BMC and analyses confounder adjusted for cohort and mother smoking third trimester.

BMC, bone mineral content; DXA, dual-energy X-ray absorptiometry; ICS, inhaled corticosteroid.

The primary limitation of our study is that it is not an RCT. However, a long-term RCT trial at 0–6 years of age with ICS would be difficult to conduct both for practical and ethical reasons; hence prospective standardised observational studies like this are needed.

Comparing different types of ICS can be difficult and some studies found that in nominally equal doses FP produces less significant growth suppression than BUD.^{9 26 43} Differences in potency between BUD (COPSAC₂₀₀₀) and FP (COPSAC₂₀₁₀) have been corrected for by calculating equipotent doses and cohort stratification.

Interpretation

After 1 year's cessation of ICS use, we did not find any significant effects on height nor BMC by age 6 even after several years of ICS treatment. This is a clinically reassuring result considering the large number of young children treated with ICS. In the subgroup of children having received the largest cumulative dose of ICS, and still receiving ICS in the sixth year, we observed a height difference of –1.16 cm.

Comparing our results with other studies is challenging since design, age group, duration and ICS treatment algorithms differ. In line with our results, one long-term RCT in young children (2 years of ICS treatment in children 2–3 years at assignment (n=285)), showed an overall 1.1 cm reduced height immediately after the treatment period.^{6 16} After 1 year of discontinuation of medication the height increase relative to baseline was 0.7 cm less (compared with the placebo group) and after 2 years the effect was only observed in a subgroup of children with lower weight (<15 kg) at enrolment.^{6 16} In our study, the association between ICS use and height was not statistically stronger in low weight children.

One long 'real-life' study in children followed from age 3 to 8 years (n=284) did not find any association between ICS use and a height difference in pre-pubertal children with asthma.¹⁵ This, however, was not controlled for confounders, dosing regimens, steroids or devices used. Another observational study of children aged 3–16 years using ICS for more than a year (n=124) also did not find any association between use of ICS and height difference, but the wide spread in ages makes this difficult to interpret.¹⁹ Finally, one observational study of children reaching adult height and a mean of 9.2 years of ICS treatment (n=211), showed no reduced adult height compared with a standard analyses from a reference population although reduced growth rates after the first years of treatment. Again this result might be affected by differences in steroid, dosing and device.²⁰

In older children, a large RCT (n=1041) of children aged 5–12 years treated 4–6 years with ICS, the mean increase in height in the ICS group was 1.1 cm less than the placebo group within the first year of treatment.¹⁷ This initial decrease in attained height persisted as a reduction in adult height.¹⁸ In light of these results it is possible, that also the growth reduction seen in the group with the highest and current steroid use by age 6 in our study will persist into adulthood.

There are no published studies on the effect of ICS on bone health in young children under 6 years. A review of studies in older children aged 5 years or more concluded that there were no significant effects of standard ICS dose on bone health.^{2 44} RCTs in older children have been conflicting with one study (n=877) in children aged 5–12 years at baseline finding that the cumulative ICS dose was associated with a small decrease in bone mineral accretion in boys, but not in girls,⁴⁵ and no difference in BMD,¹⁷ while another RCT (n=136) of children aged 5–10 years with a treatment duration of 1½ year found that regular ICS treatment, but not periodic treatment, resulted in a smaller increase in BMD (compared with disodium cromoglycate).⁴⁶

After 1 year's cessation of ICS use, we did not find any significant effects on height nor BMC by age 6 even after several years of ICS treatment. This is a clinically reassuring result in light of the large number of young children treated with ICS. In the subgroup of children having received the largest cumulative dose of ICS, and still receiving ICS in the sixth year, we observed a height difference of –1.16 cm. Long-term use of ICS are known to be safer in terms

of side effects compared with oral administration, but ICS has the potential of similar side effects.^{2 47} Given that these were the children with most severe asthma and in need of long-term steroid treatment, this seems like a minor adverse effect from a clinical perspective. Also, it is unknown what effect on height untreated disease would have caused and it is also possible that these children might show catch-up growth later in life, either as catch-up growth or a prolonged growth period.

Asthma can in itself impair growth^{48–50} and bone development,⁵¹ which can make it difficult to differentiate between an asthma or an ICS related side-effect. However, the observed association between ICS use and height was unchanged after adjustment for asthma exacerbations, as measure of asthma severity, indicating that the results were not confounded by asthma severity. Potential confounding effects of asthma would be expected to result in larger observed impairments on height or bone measures in relation to ICS treatment, that is, a type-1 error. Since we did not find a persistent association between ICS use and height in children without current ICS use by age 6 years despite this potential confounder, this supports the conclusion of limited height and bone related side effects from ICS in early childhood. Given the well-known short-term impairment of growth from ICS, this also indicates that children without current ICS use experienced catch-up in height after cessation with ICS treatment, although not demonstrated directly in our study.

There is a well-known association between asthma and increased BMI, and also between ICS use and BMI as recently reported from the COPSAC birth cohorts.⁵² Since BMI in childhood as associated with increased longitudinal growth, this could result in an underestimation of ICS effects on height, but adjustment for 6-year BMI in our study did not materially affect the results.

The effect of glucocorticoids effects on the longitudinal bone growth is complex. The extent of HPA-axis suppression is dependent on factors such as dose and duration of treatment and glucocorticoids are known to inhibit growth at every level of a child's growth axis. Long-term effects from ICS on height are therefore plausible and can be through multiple mechanisms.^{53 54}

The genetic variation, SNP rs591118, in the PDGFD gene locus has been shown to modify the risk of systemic adverse effects to ICS in terms of adrenal suppression in children with asthma⁴¹ and this is to our knowledge the only replicated gene variant associated with ICS side effects. We therefore performed a supplementary analysis of interaction between this SNP and ICS exposure on 6 years height and found no significant interaction which could have supported a causal relationship with ICS treatment.

In conclusion, we found evidence that ICS use was associated with reduced height at age 6 years but only in children with continued treatment in the sixth year of life. We found no effect on BMC. This supports that ICS are generally safe to use in relation to height and BMC, also in the youngest group of children. A subgroup of children with continued use of ICS and the largest cumulative doses showed evidence of a minor height difference. The height development of this group of children into adulthood should be explored. These findings are useful for healthcare providers when deciding on treatment strategies and key when informing parents about potential unwanted side effects when treating their young children with ICS.

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ARTIGO ORIGINAL

Custo-eficácia da ventilação não-invasiva no domicílio em pacientes com doença pulmonar obstrutiva crónica

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RESUMO

Contexto A doença pulmonar obstrutiva crónica (DPOC) é uma doença crónica associada a agudizações recorrentes, que influenciam a morbilidade e a mortalidade do paciente, ao mesmo tempo que impõem um fardo significativo de recursos aos sistemas de saúde. A ventilação não invasiva (VNI) em contexto domiciliário pode ajudar a evitar internamentos, mas a evidência económica de apoio à utilização da VNI é limitada.

Métodos Uma análise de custo-utilidade baseada no modelo Markov da perspetiva do Serviço Nacional de Saúde do Reino Unido comparou a relação custo-eficácia da VNI no domicílio com os cuidados habituais para duas populações com DPOC em fase terminal; uma população com DPOC estável a iniciar o tratamento sem internamento hospitalar recente; e uma população pós-hospitalar a iniciar o tratamento após internamento hospitalar devido a exacerbação. As taxas de hospitalização em pacientes que recebem VNI ao domicílio, em comparação com os cuidados habituais, foram derivadas de estudos aleatorizados e controlados numa revisão sistemática recente. Outros parâmetros do modelo foram atualizados com evidência recente.

Resultados No limiar de £20 000 por ano de vida ajustado à qualidade (QALY), a VNI ao domicílio tem uma probabilidade de 99,9% de ser rentável numa população pós-hospitalar, mas é improvável (4%) que seja rentável numa população estável. A relação custo-eficácia adicional (RCEA) foi de £11 318/QALY ganho na população pós-hospitalar e de £27 380/QALY ganho na população estável. As estimativas de custo-eficácia foram sensíveis aos riscos de reinternamento e mortalidade a mais longo prazo e à duração do benefício da VNI. De facto, para uma Iniciativa Global para a Doença Pulmonar Obstrutiva Crónica (GOLD) estável para pacientes em fase 4, ou com maior mortalidade e riscos de exacerbação, as RCEA aproximaram-se do limiar de £20 000/QALY.

Conclusão Provavelmente, a VNI ao domicílio é rentável para pacientes pós-hospitalização, com incerteza quanto à relação custo-eficácia da VNI ao domicílio em pacientes com DPOC estáveis, nos quais se deve centrar a investigação adicional.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive lung disease often accompanied by recurring exacerbations, that lead to clinical deterioration, and when severe, require hospitalisation.¹ When comparing non-invasive ventilation (NIV) with either no ventilation or invasive mechanical ventilation in hospital settings, in the context of type two respiratory failure/acute hypercapnic respiratory failure (AHRF), but not the absence of type 2 respiratory failure (T2RF), various study designs have consistently shown better outcomes for NIV in the form of reduced inpatient mortality and length of stay.²⁻⁶

NIV may also be administered at home with or without oxygen therapy. Based on randomised controlled trials (RCTs), a previous systematic review⁷

Key messages

What is the key question?

► Taking into account recently published evidence on effectiveness, what is the longer-term cost-effectiveness of domiciliary non-invasive ventilation (NIV) in posthospitalised and stable patients.

What is the bottom line?

► Health economic decision modelling found that domiciliary NIV is highly, likely to be cost-effective in posthospitalised patients, but unlikely to be cost-effective in stable patients, compared with usual care.

Why read on?

► Currently, there is uncertainty surrounding the effectiveness and cost-effectiveness of domiciliary NIV, and commissioning of this intervention varies across and within countries (including the UK). This paper reports an updated model-based analysis of the cost-effectiveness of domiciliary NIV for end stage COPD, incorporating new effectiveness evidence.

found no evidence for a survival benefit and limited evidence for fewer hospitalisations in stable populations. A survival benefit was also not demonstrated for posthospitalised patients (those recently discharged from admission to hospital for an exacerbation) with inconsistent findings on hospital readmissions.

We have previously demonstrated in a model-based cost-effectiveness analysis considerable uncertainty regarding cost-effectiveness of domiciliary NIV for both stable and posthospital patients.⁷ The analysis was sensitive to assumptions regarding the strength and duration of treatment effect. As a consequence of the uncertainty over evidence, commissioning of domiciliary NIV varies across and within countries (including the UK), and a robust model could aid formation of national guidance and streamline processes surrounding this treatment in the UK.

There is growing evidence relating to the effectiveness of domiciliary NIV in COPD.¹ This paper reports an analysis of the cost-effectiveness of domiciliary NIV for end-stage COPD updating our previously published model⁷ with estimates of clinical effectiveness including recent and previously missed evidence.⁸ Other model parameters are updated using real-life COPD data from the UK, including the National COPD audit⁹ and Clinical Practice Research datalink,¹⁰ which provide robust UK baselines of COPD outcomes for an untreated population.



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METHODS

Two cost-utility analyses were undertaken comparing domiciliary NIV with usual care for two COPD populations:

- Patients starting domiciliary NIV in a stable state, where they had no recent exacerbations, hospital admissions or other major change in clinical parameters over a defined period (4 or more weeks).⁷
- Patients starting domiciliary NIV immediately following admission to hospital for an exacerbation.

A Markov cohort model was constructed in TreeAge Pro (TreeAge Software, 2019) to estimate quality-adjusted life years (QALYs) and costs from the UK National Health Service (NHS) perspective. A 10-year time horizon was selected owing to high mortality in this patient population, with monthly time cycles. QALYs and costs were discounted at 3.5% as per UK guidance¹¹ with half-cycle correction performed. Model results are predicated on the benefit of NIV being accrued via a reduced risk of hospitalisation and associated cost-savings, life years gained and utility improvements.

Model population

The stable model population was reflective of stable patients included in RCTs from the clinical effectiveness systematic review.⁸ The mean age was 67, 54% were female, and 52% smokers (online supplemental appendix 1). Distribution between 2011 GOLD stages was not commonly reported, therefore an assumption was made that 50% were in Global Initiative for Chronic Obstructive Lung Disease (GOLD) severity stage 3 and 50% in stage 4, and domiciliary NIV would not be required in earlier disease stages, or where significant comorbid disease contributed to the underlying respiratory failure. COPD stage was defined according to 2011 GOLD classifications; GOLD stage 3 had a predicted forced expiratory volume in one second (FEV_1) $\geq 30\%$, $<50\%$ and GOLD stage 4 a predicted $FEV_1 \leq 30\%$. As real-world information was available for posthospital patients, the model population was reflective of patients in the 2017 National UK COPD audit,⁹ mean age 73, 47% female, 31% smokers, with an assumed 50% in GOLD stage 3 and 4 (online supplemental appendix 1). Online supplemental appendix 2 details all model assumptions.

Model structure

Figure 1, adapted from Dretzke *et al*,⁷ shows the model composition. The same structure was used for both populations, although posthospitalised patients started in 'postdischarge month 1', while

stable patients began in stable states. The model used tunnel states to represent increased risk of mortality and readmission, lower quality of life, and higher costs, in those discharged after admission for an exacerbation. Accordingly, patients could not remain in postdischarge states by definition. Posthospitalised patients moved to stable health states after the postdischarge period, and stable patients moved to a posthospital state if they experienced an exacerbation requiring hospitalisation. There was a differing mortality risk in each state, according to population and health state. Patients could transition from GOLD stage 3–4, although not 4–3 as the disease is progressive. Online supplemental appendix 3 provides further detail.

Model parameter estimates

Table 1 presents the model parameters for hospitalisation, mortality and discontinuation.

Hospitalisation and mortality in postadmission health states

Transition probabilities for mortality and readmission for postdischarge states in both populations were obtained from the most recent UK audit of patients with COPD admitted to hospital.⁹ Risk of readmission and mortality were assumed (1) to be evenly distributed over the 3-month period, and (2) to not to differ by GOLD stage as there is no evidence on a differentiated risk.⁷

Hospitalisation and mortality risks for the posthospital population

Beyond the postdischarge period for the posthospitalised population, there was greater uncertainty regarding admission rates and mortality. Four studies^{12–15} were identified which reported long-term admission rates and mortality. Highest and lowest rates were used in sensitivity analyses, with mid-range rates used for the base case.

COPD-related mortality was captured via the risk of a COPD-related death either during admission or in the 3-month postdischarge period.⁹ These risks in combination with the all-cause mortality risk reported in Garcia-Aymerich *et al*¹² were assumed to stay constant over the cohort lifetime.

Exacerbation and hospitalisation risk in stable health states

For the stable population, data on exacerbation and hospital admissions in the stable health states were drawn from a large UK study (n=12 830) with long-term follow-up of a COPD general practice population.⁹

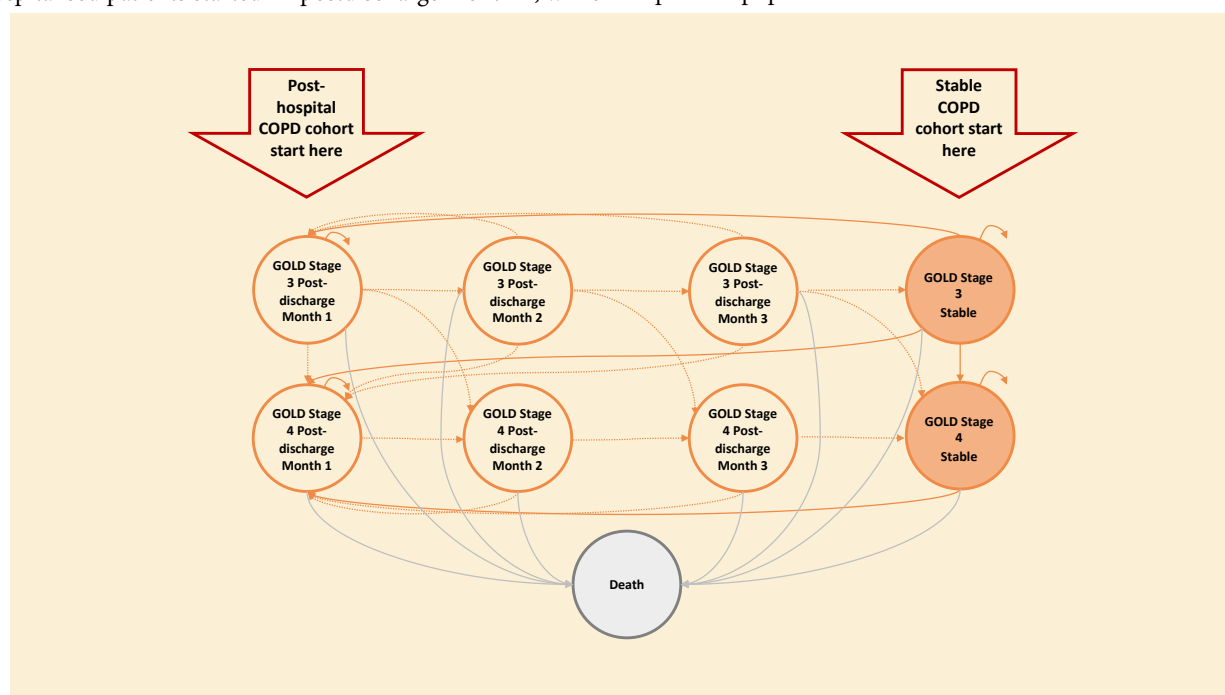


Figure 1 State-transition schematic. GOLD, Global Initiative for Chronic Obstructive Lung Disease.

Table 1 Hospitalisation, mortality and discontinuation parameters**Mortality and hospitalisation in postadmission states**

Definition	Probability	Beta distribution, α , β	Source
COPD-related death during admission			2017 National UK COPD audit ⁹
Men	0.046	654, 13 552	
Women	0.035	570, 15 514	
COPD-related 90-day death post admission			2017 National UK COPD audit ⁹
Men	0.073	1043, 13 163	
Women	0.066	1058, 15 027	
90-day COPD-related readmission			2017 National UK COPD audit ⁹
Men	0.171	2423, 11 784	
Women	0.162	2609, 13 476	
All-cause COPD mortality post admission			2017 National UK COPD audit ⁹
90-day men	0.046	650, 13 556	
90-day women	0.041	660, 15 425	

Hospitalisation rate and risk of non-COPD-related mortality in the stable health state for the post hospital population

Definition	Rate	Sample size	Source
Base case			Garcia-Aymerich <i>et al</i> ¹²
COPD admissions per year	1.6	340	
Non-COPD-related mortality	0.071	340	
Lowest rates			Bucknall <i>et al</i> ¹⁴
COPD admissions per year	0.47	464	
Non-COPD-related mortality	0.194	464	
Highest rates			Budweiser <i>et al</i> ¹³ and Heinemann <i>et al</i> ¹⁵
Base case risks multiplied by 2			

Treatment and exacerbation rates for stable population

Severity stage	Annual exacerbation rate	Proportion of exacerbations hospitalised		Source
		%	Beta distribution, α , β	
GOLD 3	2.356	10.2	2267, 22 062	Rothnie <i>et al</i> ¹⁰
GOLD 4	2.914	13.4	862, 6429	Rothnie <i>et al</i> ¹⁰

Base case rate ratios for admission to domiciliary NIV relative to usual care

	Rate Ratio (95% CI)*	Source
All studies estimates		
Posthospital population		
Pooled mean	0.494 (0.382 to 0.638)	Pooled result of 11 RCTs ⁸
Best-case NIV	0.333 (0.187 to 0.596)	Li <i>et al</i> ³⁰
Worst-case NIV	1.372 (1.067 to 1.763)	Struik <i>et al</i> ³¹
Stable population		
Pooled mean	0.606 (0.482 to 0.760)	Pooled result of 10 RCTs ⁸
Best-case NIV	0.346 (0.276 to 0.433)	Luyang <i>et al</i> ³²
Worst-case NIV	1.166 (0.601 to 2.264)	Kamiński <i>et al</i> ³³
Western setting estimates†		
Posthospital population		
Pooled mean	0.728 (0.212 to 2.504)	Pooled result of 2 RCTs ⁸
Best-case NIV	0.389 (0.321 to 0.470)	Murphy <i>et al</i> ¹
Worst-case NIV	1.372 (1.067 to 1.763)	Struik <i>et al</i> ³¹
Stable population		
Pooled mean	0.718 (0.617 to 0.836)	Pooled result of 4 RCTs ⁸
Best-case NIV	0.643 (0.432 to 0.956)	Clini <i>et al</i> ³⁴
Worst-case NIV	1.166 (0.601 to 2.264)	Kaminski <i>et al</i> ³³

Discontinuation

Health state	Discontinuation Rate	Normal distribution, 95% CI	Source
All patients	15%	10% to 20%	Assumption and Dretzke <i>et al</i> ⁸

*Western settings included studies from Italy, Poland, the Netherlands, Germany and the UK. Non-Western studies contributing to meta-analyses are set in China.

†Natural log rate ratios and standard errors used in the probabilistic sensitivity analysis are shown in online supplemental appendix 6.

GOLD, Global Initiative for Chronic Obstructive Lung Disease; NIV, non-invasive ventilation; RCT, randomised controlled trial.

Table 2 Utility scores and costs for stable GOLD states, and costs of providing a domiciliary NIV service

	Utility GOLD stage 3	Utility GOLD stage 4	
Sample size	299	37	
Mean utility score (SE)	0.678 (0.015)	0.601 (0.042)	
Type of healthcare	Cost GOLD stage 3	Cost GOLD stage 4	
Routine healthcare	£39.91/month	£77.33/month	
Routine pharmacotherapy	£50.42/month	£54.71/month	
Moderate exacerbation	£140.40 per episode		
Severe exacerbation	£2283.18 per episode		
Estimation of the cost of providing a domiciliary NIV service			
Cost type	Cost	Unit cost source	Resource use source
Equipment costs			
NIV equipment for domiciliary use	£2939.69	Supplier estimates	Clinician estimates of use of machines and cost estimate from firms
NIV equipment for domiciliary use monthly cost	£48.99	Depreciated over 5 years	
Set-up costs			
NIV set-up and assessment month 1	£482.82	National Tariff Payment System 2019/20 ³⁵	Expert opinion
NIV Follow-up in m3: 1 × Consultant led outpatient app+1 × Blood gas test	£157.16 + £194	NHS reference costs 2018/2019 ³⁶	Expert opinion
Annual costs therefore			
2 × blood gas test conducted at routine follow-up	2 × £194	NHS reference costs 2018/2019 ³⁶	Expert opinion
1 x annual NIV assessment and consumable provision	£650	Estimate	Expert opinion
Monthly costs			
First 3 months	£294.32	Includes equipment and set-up costs	
>3 months	£90.58	Includes equipment and annual monitor and service costs	

GOLD, Global Initiative for Chronic Obstructive Lung Disease; NHS, National Health Service; NIV, Non-Invasive ventilation.

Mortality risks for the stable population

For health states for the stable population, Office for National Statistics life tables were used to populate age and gender-specific all-cause mortality probabilities, adjusted to avoid double counting of COPD-related mortality (online supplemental appendix 4).

Discontinuation rate

After an initial period, it was assumed a proportion of patients starting domiciliary NIV would discontinue treatment. Non-adherence and discontinuation rates vary across both populations,⁸ therefore it was assumed that 15% of patients would discontinue after 3 months. Patients who discontinued NIV were assumed to incur costs but not benefits of NIV in the initial 3 months, and neither costs nor benefits of NIV beyond 3 months.

Disease progression in stable and posthospital population

Baseline risks of hospital admission and mortality need to be extrapolated beyond the follow-up duration in source studies. Accordingly, to capture long-term prognosis, patients were allowed to move between GOLD stages. Probabilities associated with moving to GOLD stage 4 were sourced from a previously published model¹⁶ and applied to GOLD stage 3 states for both populations (online supplemental appendix 5).

Effectiveness of domiciliary NIV

Hospital admission data were taken from our meta-analysis of absolute differences⁸ and converted to rate ratios by estimating the number of events and total time at risk (assuming complete follow-up) from relevant RCTs. The rate ratio and SE were calculated using Poisson regression, rate ratios with 95% CIs (table 1).

The base case analysis considered all studies in the review; however, to account for differences between healthcare systems,

a sensitivity analysis was also performed on studies in Western/high-income settings. Further sensitivity analyses used individual studies with the best-case and worst-case rate ratios for the effect of NIV on hospital admissions.

Given that hospital admission is associated with increased mortality risk, the model produces an improvement in mortality for NIV indirectly by preventing admissions. To assess external validity, the extent to which the model reflects the real-world, model survival rates were contrasted with those found in the RCTs in the clinical effectiveness systematic review.⁸

Following consultation with clinicians involved with treating patients with NIV, it was assumed that the effect of NIV in reducing admissions would last 5 years in both patient groups, with alternative periods of efficacy tested in sensitivity analysis.

Utility values

Utility values were obtained for each stable GOLD stage 3 and 4 from EQ-5D-5L (the five level EuroQol five dimensions) values for 336 participants with a confirmed diagnosis of COPD from a UK cohort study,¹⁷ table 2. No effect on quality of life is assumed above that of the impact NIV has on exacerbations and mortality, this assumption is tested in sensitivity analyses.

In line with previous COPD models,^{18–20} disutility values associated with moderate or severe exacerbation were taken from Rutten-van Mölken *et al.*²¹ A disutility of 15% for a moderate exacerbation was assigned for a period of 1 month, with a 50% loss in the first month of a severe exacerbation and a 25% loss in second and third months.

Costs

Costs were presented in 2019/2020 pounds sterling and inflated to current value using hospital and community health services index and NHS cost inflation index.²² Costs were subdivided into three

Table 3 Base case analyses posthospital population

Strategy	Mean cost (£)	Mean QALY	ICER (£/QALY)	Probability cost-effective*
Base case posthospital population, all studies, pooled mean rate ratio				
Domiciliary NIV	£19 876	2.391	£11 318	99.9%
Usual care	£15 081	1.967		
Incremental difference	£4 799	0.424		
Posthospital population, 'Western' settings†, pooled mean rate ratio				
Domiciliary NIV	£19 840	2.136	£28 430	46.9%
Usual care	£15 075	1.969		
Incremental difference	£4 765	0.168		

*Cost-effective at £20 000/QALY.

†Western studies included studies reporting hospitalisations from Italy, Poland, the Netherlands, Germany and the UK.

ICER, incremental cost-effectiveness ratio; NIV, non-invasive ventilation; QALY, quality-adjusted life year.

components, (1) routine COPD care, (2) treatment of exacerbations, and (3) provision of domiciliary NIV.

All detailed cost calculations for each component can be found in online supplemental appendix 7, with table 2 providing headline costs, as well as the methodology for estimating the cost of providing domiciliary NIV, estimated at £1698.18 in the first year and £1086 in subsequent years (further details in online supplemental appendix 7).

Analyses

A cost-utility analysis was undertaken to estimate incremental cost-effectiveness ratios (ICERs), the difference in costs divided by

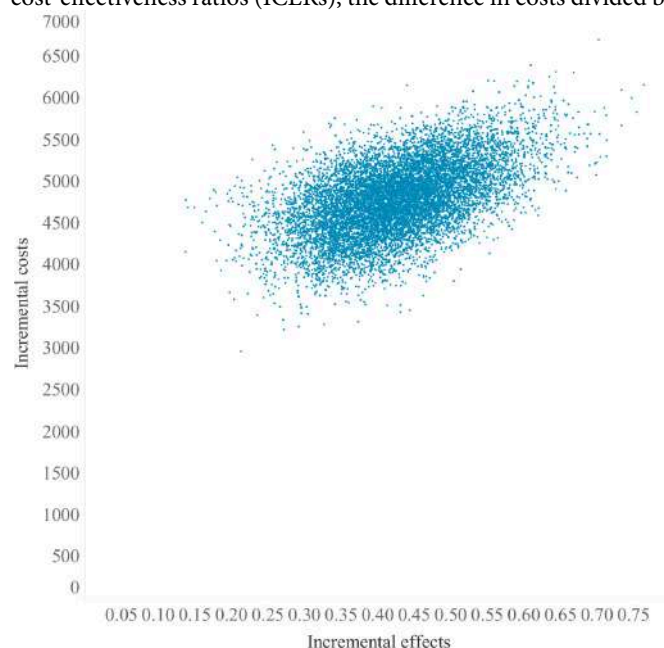


Figure 2 Base case cost-effectiveness plane for domiciliary NIV for posthospitalised patients. Incremental costs and effectiveness reflect the sum of mean costs and quality-adjusted life years (QALYs) of domiciliary non-invasive ventilation (NIV) minus those of usual care. Results are generated from probabilistic sensitivity analysis, where 10 000 unique Monte Carlo simulations sample from the known distributions of model parameters. Accordingly, each dot reflects the incremental costs and QALYs for each one of the 10 000 model iterations. Notice, all dots lie above 0 for incremental effectiveness indicating NIV is more effective, and all points above 0 for incremental costs indicating NIV is more expensive. The size of the cloud of dots reflect the range of incremental costs and QALYs that the model results could take, given the uncertainty in the model parameters.

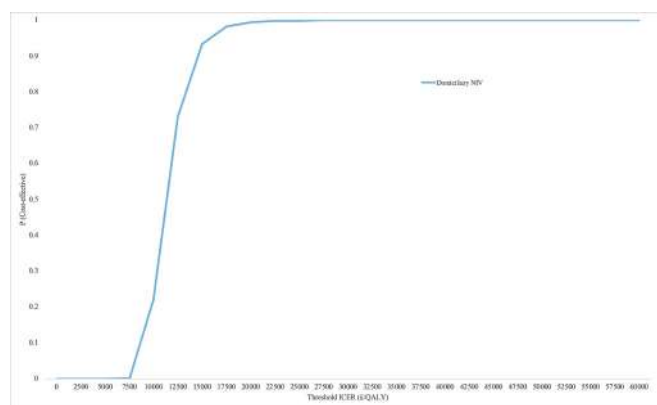


Figure 3 Base case cost-effectiveness acceptability curve. The graph plots the probability that domiciliary NIV is cost-effective at various UK thresholds for willingness to pay for 1 QALY (£/QALY). Between the commonly used UK thresholds of £20 000 to £30 000 per QALY, it can be seen NIV is consistently 99%–100% likely to be cost-effective. ICER, incremental cost-effectiveness ratio; NIV, non-invasive ventilation; P, probability; QALY, quality-adjusted life year.

the difference in QALYs of two strategies, with results presented as cost-per-QALY gained. Cost-effectiveness was considered in relation to the lower NICE threshold of £20 000 per-QALY gained.²³ Each result reflects mean costs and QALYs as an average of 10 000 model iterations generated by probabilistic sensitivity analysis, used to account for parameter uncertainty. Where possible, distributions were attached to probabilities, utilities and costs in the model. Beta distributions were attached to transition probabilities and utilities, with natural logs of rate ratios sampled normally and exponentiated.²⁴ The model results were expressed as a cost-effectiveness acceptability curve (CEAC) showing graphically the probability of cost-effectiveness of domiciliary NIV across a range of cost-per-QALY thresholds.²⁴ Deterministic sensitivity analyses were used to assess the individual impact of varying model parameters on cost-effectiveness results.

Expected value of perfect information (EVPI)

EVPI is a quantitative method of assessing the marginal value of further studies, and in essence helps consider whether it is worth conducting more research.²⁵ In order to calculate the population EVPI the size of population expected to benefit must be calculated. We estimated this to be 661 199 for stable patients and 190 049 for posthospital patients over a 10-year time horizon (calculations in online supplemental appendix 8).

RESULTS

Posthospital population

Base case for the posthospital population

In the base case analysis for the posthospital population domiciliary NIV was £4799 more costly, delivering 0.424 more QALYs, making the ICER £11 318/QALY gained. This was 99.9% likely to be cost-effective at the £20 000/QALY threshold (table 3).

Using hospitalisation rates from Western studies, QALY gains reduced to 0.168 for £4765 additional cost, increasing the ICER to £28 430/QALY with domiciliary NIV only 46.9% likely to be cost-effective.

The base case cost-effectiveness plane in figure 2 shows NIV is more effective and costly in all model iterations (hence all iterations in the north-east quadrant). The corresponding CEAC (figure 3) demonstrates domiciliary NIV is very likely to be cost-effective over thresholds of about £12 500/QALY and is always cost-effective between £20 000/QALY and £30 000/QALY.

Sensitivity analysis

Table 4 shows the impact of alternate parameter values on cost-effectiveness in posthospital patients. Applying the rate ratio for hospital admissions from the worst-case study results in NIV being

Table 4 One-way sensitivity analysis in the posthospital population

	Cost difference (£)	QALY difference	ICER (£/QALY)	Probability cost-effective*
Varying the rate ratio				
Best-case NIV	+£4855	+0.596	£8146	100%
Worst-case NIV	+£4715	−0.220	Dominated	1.1%
Base case	+£4799	+0.424	£11 318	99.9%
Best case 'Western' settings NIV†	+£4765	+0.539	£8979	100%
Worst-case 'Western' settings NIV†	+£4687	−0.215	Dominated	0%
Change in utility on NIV				
+0.20 utility	+£4799	+1.005	£4763	100%
+0.10 utility	+£4799	+0.714	£6707	100%
+0.05 utility	+£4799	+0.571	£8385	100%
−0.05 utility	+£4799	+0.280	£17 104	71.1%
−0.10 utility	+£4799	+0.135	£35 526	5.4%
−0.20 utility	+£4799	−0.158	Dominated	0%
Varying duration of effect				
2 years	+£4813	+0.218	£22 078	26.0%
5 years (base case)	+£4799	+0.424	£11 318	99.9%
10 years (model horizon)	+£4172	+0.535	£7798	99.9%
Alternate model time horizon				
2 years	+£919	+0.073	£12 589	78.9%
5 years	+£2187	+0.260	£8408	99.5%
10 years (base case)	+£4799	+0.424	£11 318	99.9%
20 years	+£5763	+0.484	£11 914	99.4%
Alternate Mortality and readmission risk				
Lower risks from Bucknall <i>et al</i> ¹⁴	+£3715	+0.173	£21 473	39.34%
Doubling all mortality risks ^{13 15}	+£3953	+0.400	£9883	99.9%

*Cost-effective at £20 000/QALY.

†Western studies included studies from Italy, Poland, the Netherlands, Germany, and the UK.

ICER, incremental cost-effectiveness ratio; NIV, non-invasive ventilation; QALY, quality-adjusted life year.

dominated, that is both more costly with worse health outcomes in all study settings. Assuming the duration of effect of domiciliary NIV in reducing hospital admissions is only 2 years, gives a higher ICER of £22 078/QALY, with likely cost-effectiveness reduced to 26%. However, it would take a 0.10 reduction in utility on NIV to significantly impact the likely cost-effectiveness, resulting in an ICER of £35 526/QALY and only 5% likely to be cost-effective.

Changing baseline hospitalisation and mortality data to lower estimates¹⁴ increased the ICER to £21 473/QALY and reduced the probability of NIV being cost-effective to 39%. However, increasing all mortality risks by a factor of two decreased costs and outcomes owing to shorter survival, reducing the ICER to £9883/QALY.

Table 5 Base case analyses stable population

Strategy	Mean cost (£)	Mean QALY	ICER (£/QALY)	Probability cost-effective*
Base case stable population, all studies, pooled mean rate ratio				
Domiciliary NIV	£25 461	4.177	£27 380	4%
Usual care	£16 973	3.867		
Incremental difference	£8488	0.310		
Stable population, 'Western' settings†, pooled mean rate ratio				
Domiciliary NIV	£25 373	4.007	£60 000	25%
Usual care	£16 973	3.867		
Incremental difference	£8400	0.14		

*Cost-effective at £20 000/QALY.

†Western studies included studies reporting hospitalisations from Italy, Poland, the Netherlands, Germany and the UK.

ICER, incremental cost-effectiveness ratio; NIV, non-invasive ventilation; QALY, quality-adjusted life year.

Varying the time horizon did not impact cost-effectiveness significantly, neither did analyses on various machine costs, lifespans, maintenance cost of NIV (online supplemental appendix 9) or different population subgroups (online supplemental appendix 10).

In terms of model validity, base case estimated mortality at 2 years was 43.5% on usual care and 36% on NIV, this is similar to an RCT which reported 2-year mortality at 40% in posthospitalised patients receiving NIV.²⁶ Moreover, the relative risk of mortality on NIV compared with usual care of 0.83 is statistically similar to the relative risk of mortality for the posthospitalised population found in RCTs in the systematic review 0.78 (0.60–1.03).⁸

EVPI for the posthospital population

The EVPI for the posthospital population was estimated to be £3.25 per patient, reflecting low uncertainty in the base case analysis at a threshold of £20 000/QALY. The estimated population EVPI over the next 10 years was estimated at £617 659.

Stable population

Base case

In the base case analysis for the stable population, domiciliary NIV was £8488 more costly but gave 0.310 additional QALYs, for an ICER of £27 380/QALY, only 4% likely to be cost-effective at the £20 000/QALY threshold (table 5). Using a rate ratio estimate from 'Western' settings, saw a smaller QALY gain of 0.14 for £8400 additional cost, increasing the ICER to £60 000/QALY. The likely cost-effectiveness was 25% due to uncertainty in the effectiveness estimate.

The base case cost-effectiveness plane (figure 4) shows NIV was more effective and costly in most model iterations. The corresponding CEAC (figure 5) demonstrates QALY increases come at

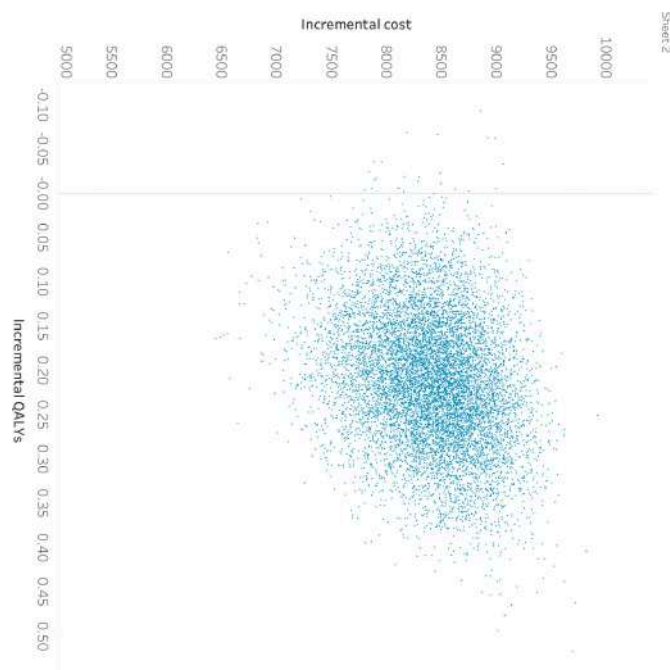


Figure 4 Base case cost-effectiveness plane for domiciliary NIV for stable patients. Incremental costs and effectiveness reflect mean the sum of mean costs and quality-adjusted life years (QALYs) of domiciliary non-invasive ventilation (NIV) minus those of usual care. Results are generated from probabilistic sensitivity analysis, where 10 000 unique Monte Carlo simulations sample from the known distributions of model parameters. Accordingly, each dot reflects the incremental costs and QALYs for each one of the 10 000 model iterations. Notice, all dots lie above 0 for incremental effectiveness indicating NIV is more effective, and all points above 0 for incremental costs indicating NIV is more expensive. The size of the cloud of dots reflect the range of incremental costs and QALYs that the model results could take, given the uncertainty in the model parameters.

a high cost, with domiciliary NIV only likely to be cost-effective over thresholds of £40 000/QALY.

Sensitivity analyses

Table 6 shows sensitivity analyses for stable patients. When using alternate rate ratios, NIV is almost certain to be cost-effective at £20 000/QALY in the best case all studies estimate, whereas the best-case Western study only gives an ICER of £31 196/QALY. Cost-effectiveness was very sensitive to changes in utility, with a +0.05 gain in utility on NIV reducing the ICER to below £20 000/QALY. While assuming the effect of NIV lasted for a 10-year time horizon also reduced the ICER to £19 119/QALY.

Domiciliary NIV is more cost-effective in patients with higher baseline hospitalisation and mortality risks. Higher baseline hospitalisation and mortality risks¹² reduced the ICER to £20 797/QALY, increasing the probability of NIV being cost-effective to 44%.

Sensitivity analyses on alternative machine cost, lifespan and annual NIV maintenance cost did not influence cost-effectiveness (online supplemental appendix 9).

Choice of GOLD stage starting cohort also influenced the likely cost-effectiveness, the ICER fell to £21 132/QALY with a 43% probability of being cost-effective when only GOLD stage 4 patients were considered. Results for other subgroups were similar to the base case (online supplemental appendix 10).

EVPI analysis for the stable population

The EVPI per patient for the posthospital population was estimated to be £18.01 per patient and over the next 10 years generated population EVPI of £11 908 194.

DISCUSSION

This updated and enhanced economic model for domiciliary NIV in severe patients with COPD provides evidence on the likely

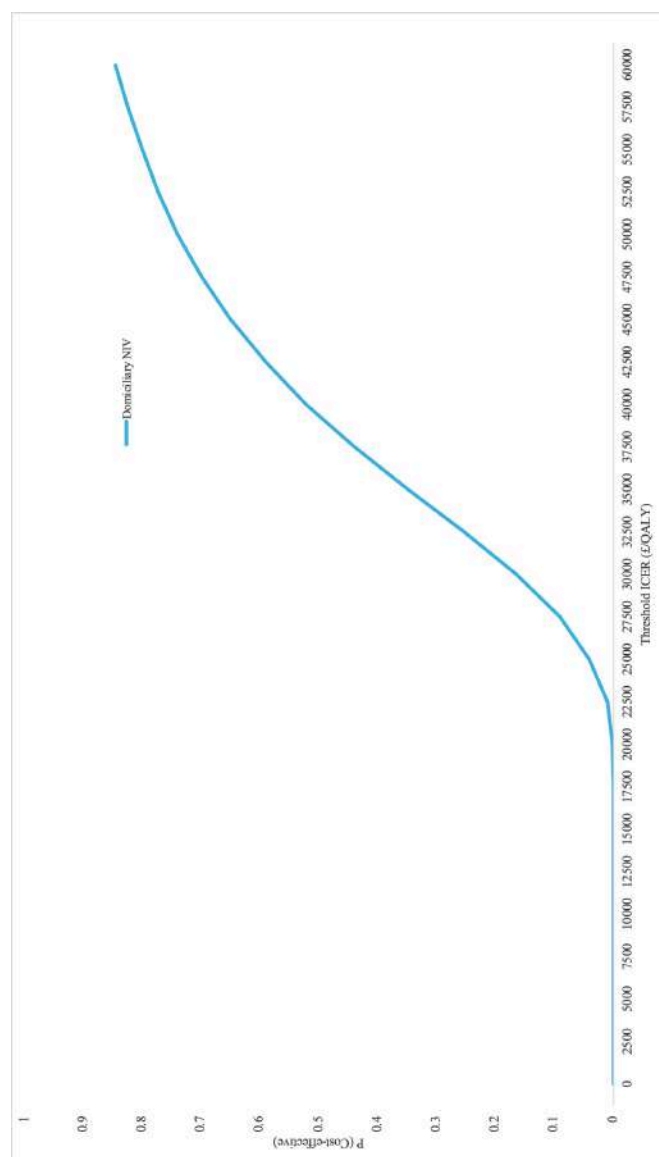


Figure 5 Base case cost-effectiveness acceptability curve. The graph plots the probability that domiciliary NIV is cost-effective at various UK thresholds for willingness to pay for 1 QALY (£/QALY). Above thresholds of £40 000 per QALY, it can be seen NIV emerges as likely to be cost-effective. ICER, incremental cost-effectiveness ratio; NIV, non-invasive ventilation; P, probability; QALY, quality-adjusted life years.

cost-effectiveness of domiciliary NIV in a posthospital population. The high likelihood of cost-effectiveness in the posthospitalised population is driven by favourable new evidence on hospital admissions from recently published RCTs, and those conducted in China not included in previous systematic reviews.⁸ However, caution is required for generalisation to the UK, as the likely cost-effectiveness is below 50% when applying estimates of NIV effect from 'Western' studies. While NIV for those with more stable disease is unlikely to be cost-effective, the ICER for stable patients in GOLD stage 4 and with higher exacerbation risks was only just over the £20 000/QALY threshold.

Are there settings in which domiciliary NIV is more cost-effective?

Cost-effectiveness and clinical effectiveness are related, in that groups with the most clinical benefit will usually incur lower costs, and this is the case with domiciliary NIV. Analyses on admissions and mortality risks demonstrated that posthospitalised patients, who have inherently higher admission and mortality risks, are more likely to benefit from domiciliary NIV.

The rate ratio in posthospitalised populations in 'Western' settings, derived from fewer studies, was also higher than the all-studies estimate and lowered the likely cost-effectiveness

Table 6 One-way sensitivity analysis for stable population

	Cost difference (£)	QALY difference	ICER (£/QALY)	Probability cost-effective*
Varying the rate ratio				
Best-case NIV	+£8804	+0.562	£15 665	99.2%
Worst-case NIV	+£8112	−0.111	Dominated	0%
Base case	+£8488	+0.310	£27 380	4%
Best-case 'Western' setting NIV†	+£8812	+0.271	£31 196	8%
Worst-case 'Western', setting NIV†	+£8112	−0.111	Dominated	0%
Change in utility on NIV				
+0.20 utility	+£8488	+1.147	£7401	100%
+0.10 utility	+£8488	+0.72	£11 597	100%
+0.05 utility	+£8488	+0.514	£16 514	82.4%
Base case	+£8488	+0.310	£27 380	4%
−0.05	+£8488	+0.097	£87 505	0%
Varying duration of effect				
2 years	+£8488	+0.150	£56 153	0%
10 years (model horizon)	+£7896	+0.413	£19 119	58%
Alternate model time horizon				
2 years	+£2057	+0.033	£62 333	0%
15 years	+£10 696	+0.392	£27 286	3%
20 years	+£11 750	+0.429	£27 389	3%
Alternate mortality and readmission risk				
Higher risks from Garcia-Aymerich <i>et al</i> ¹²	+£5137	+0.247	£20 797	44%

*Cost-effective at £20 000/QALY.

†Western studies included studies reporting hospitalisations from Italy, Poland, The Netherlands, Germany and the UK
ICER, incremental cost-effectiveness ratio; NIV, non-invasive ventilation; QALY, quality-adjusted life year.

somewhat, suggesting other factors might be influencing outcomes independently of NIV in 'Western' settings. Assuming that NIV only impacts hospital admissions for a duration of 2 years also raises the ICER over the £20 000/QALY threshold. Long-term registry-based studies of domiciliary NIV might assist in generating the data to estimate how long the true effect lasts.

Domiciliary NIV for stable populations is not likely to be cost-effective at the £20 000/QALY threshold. However, there is evidence that patients with a higher risk of mortality and admission are more likely to benefit from domiciliary NIV, and it remains possible that stable populations such as those with a high blood CO₂ level²⁷ would benefit more. However, sensitivity analyses based on severe hypercapnia, or change in hypercapnia with treatment, were not possible because of poor reporting, and a lack of studies targeting appropriate patients.

How certain are the results?

The probability of cost-effectiveness in posthospital populations is close to 100% at the £20 000 per QALY threshold; however, there is more uncertainty in stable patients. Cost-effectiveness of NIV in the posthospital population is higher (99.9%) than in our original model (72%) reflecting reduced uncertainty. However, the ICER is actually higher (£11 318/QALY vs £10 107/QALY) as the time horizon and NIV effect duration were lowered to 10 years and 5 years, respectively, reflecting greater knowledge of long-term outcomes. The result in the stable population is sensitive to assumptions, for example, applying an increase in utility of 0.05 on NIV lowers the ICER below the £20 000/QALY threshold, and using the best-case rate ratio estimate results in the intervention being close to 100% cost-effective at the £20 000/QALY threshold.

What studies should be done next?

One of the limitations of our study concerns the pooling of data from potentially heterogeneous patients with COPD, and clearly given the sensitivity to variation in clinical risk there could be

real value in exploring the effect of NIV in these subgroups. In particular, the estimate for the value of further research in the stable population is substantial, reflecting the sizeable population expected to benefit. However, uncertainty regarding mortality and readmission rates, which are shown to influence cost-effectiveness in both populations, is not parameterised in this model (and therefore excluded from the EVPI) owing to the lack of consistency, and ought to be a target for further research. More nuanced studies enrolling subgroups of patients with COPD in the stable state, for example, studies targeting specific subgroups within a stable population, for example, severely hypercapnic patients (eg, pCO₂>7.5 kPa), and studies using higher pressure settings²⁸ and longer-term follow-up could reduce uncertainty in future cost-effectiveness evaluations. Moreover, research will be required to understand the long-term impact of the COVID-19 pandemic on patient with COPD outcomes and treatment patterns, and may require updated modelling to reflect the new normal.

Strengths and limitations

Key strengths of this analysis derive from the original model design, which considers stable and posthospital patients with COPD separately, allowing for appropriate risk estimates for each population. Moreover, the utilisation of postadmission health states allows higher risks of readmission and mortality in patients with COPD immediately after discharge. Results are strengthened by the updating of model parameters using recently published data.

Moreover, the use of more robust assessment of clinical effectiveness evidence has decreased the uncertainty regarding the treatment effect of NIV (hospital admissions) in posthospital patients. This has arisen from the incorporation of a large number of additional studies and the decision to use a pooled effect estimate, despite some evidence of heterogeneity. This was felt to be a reasonable decision in this case as the direction of effect was consistent (bar one study), unlike the original analysis which was limited to three studies with substantial uncertainty around

direction of effect. The degree of uncertainty regarding the pooled estimate in the stable population has also been reduced, driven by the inclusion of previously unidentified studies conducted in China. The inclusion of evidence from studies conducted worldwide strengthens the overall cost-effectiveness findings, although the generalisability of these findings to different healthcare settings needs further evaluation.

However, the analyses cannot overcome uncertainties in parameters, in particular for the longer-term risks where there is only limited evidence. Nonetheless, this analysis provided extensive sensitivity analyses to illuminate the implications of this uncertainty wherever possible.

It is possible our dichotomisation of stable and posthospital patients reflects more the pathway by which hypercapnia is identified than different populations, further research is required. Importantly, patients with COPD are mainly monitored for respiratory failure using oxygen saturations, and rarely blood gases, when stable. This may lead to late identification of stable hypercapnia, whereby it is only deterioration with resultant acidosis and hospital admission that leads to blood gas being taken during admission and at follow-up. Research to date to identify factors predicting hypercapnia has been unable to identify accurately all those who might require blood gas testing, but those with severe disease and with a prior admission (even if not requiring NIV) may be an important group.²⁹ Alternatively, they may be truly different due to medical optimisation while admitted, or other as yet unknown factors.

CONCLUSION

Domiciliary NIV appears to be cost-effective when started immediately after or within 4–6 weeks of a hospital admission in which NIV was required. Cost-effectiveness is greater in more severely ill patients, and in those with a higher risk of mortality or subsequent admission. Uncertainty remains around the cost-effectiveness of domiciliary NIV in stable patients with COPD, as well as patients within a stable population that might benefit most, and further research should focus on this area.

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Contributors JH edited the existing model, updated model parameters, conducted statistical analyses, performed the economic analysis and wrote the paper with guidance from SJ, AMT, JD and DM. SJ designed the original health economic analyses, supervised the economic modelling and contributed to writing the paper. AMT provided clinical guidance on and identified the updated model parameters and contributed to writing the paper. JD and DM designed the systematic review from which the hospitalisation data was drawn, advised on use of parameters in the economic model and contributed to the writing of the paper. JD led and undertook the systematic review. SJ is the guarantor and accepts full responsibility for the work and the conduct of the study, and controlled the decision to publish.

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Relação custo-eficácia da gestão dos cuidados ambulatoriais de pneumotórax espontâneo primário: um ensaio aleatorizado, controlado e aberto

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RESUMO

Contexto A gestão em ambulatório de pneumotórax espontâneo primário tem demonstrado reduzir a hospitalização inicial, mas à custa do aumento de eventos adversos. Como resultado, subsistem questões sobre a relação custo-eficácia desta opção.

Objetivos Foi realizada uma avaliação económica em ensaio em paralelo com um ensaio controlado aleatorizado de modo a avaliar a relação custo-eficácia do cuidado ambulatório comparativamente à gestão baseada em orientações padrão.

Métodos Os pacientes foram atribuídos aleatoriamente ao tratamento com um dispositivo ambulatório ou a uma gestão baseada em orientações padrão (aspiração, inserção de tubo torácico padrão ou ambos). O seguimento consistiu em 12 meses. Os resultados incluíram o uso e os custos dos recursos de cuidados de saúde, a qualidade de vida, os anos de vida ajustados à qualidade (QALY) e a relação custo-eficácia.

Resultados Foram recrutados 236 pacientes e atribuídos aleatoriamente a cuidados ambulatoriais (n=117) e cuidados padrão (n=119). Após múltiplas imputações por dados em falta, os pacientes do grupo de cuidado ambulatório apresentaram custos de saúde do Serviço Nacional de Saúde significativamente mais baixos (-£788, diferença de IC 95%: -1527 a -50; p=0,037) do que os pacientes do grupo de cuidado padrão. Não se registaram diferenças no número de QALY ganhos (diferença média: -0,001, diferença IC 95%: -0,032 a 0,030; p=0,95). Quando os cuidados padrão foram comparados com os cuidados ambulatoriais, a relação custo-eficácia adicional foi de £799 066 por QALY ganho, bem acima dos limiares atuais de custo-eficácia. Como resultado, a probabilidade de os cuidados ambulatoriais serem rentáveis foi de 0,93.

Conclusão É altamente provável que a gestão em ambulatório seja uma opção rentável na gestão do pneumotórax primário.

Número de registo do ensaio ISRCTN79151659.

INTRODUCTION

Pneumothorax is a common clinical problem, occurring in approximately 3000 patients per year in the UK.^{1,2} Most patients require an intervention to re-expand the lung and more than half of patients subsequently requiring the insertion of a chest tube.³ This results in hospital stays of up to 8 days⁴ and so the cost of treating pneumothorax can be considerable.

Therefore, interventions that remove the need for long hospital admissions, such as ambulatory management, could provide a highly cost-effective alternative to hospital treatment and admission. The recent Randomised Ambulatory Management of Primary Pneumothorax (RAMPP) trial showed that ambulatory care resulted in a significant decrease in hospital stays (median 0 vs 4 days) when compared with standard guideline-based management (ie, aspiration, drainage or both).⁵ However, this positive finding was at the expense of increased adverse events, some of which were serious, and required regular review of patients. This, coupled with the fact that pleural vent kits for use in ambulatory care

Key messages

What is the key question?

► Ambulatory management of primary spontaneous pneumothorax (PSP) has been shown to reduce initial hospital stay over aspiration and/or drainage at the expense of increased adverse events. This raises concerns on whether the benefits of ambulatory care are offset by increases in healthcare use over the longer term.

What is the bottom line?

► This is the first randomised controlled trial that evaluates the cost-effectiveness of ambulatory care management when compared with standard guideline treatment showing that ambulatory management is cost-effective.

How this study might affect research, practice or policy

► These data suggest that PSP can be cost-effectively managed for outpatients, using ambulatory devices in those who require intervention.

are relatively costly (£212 each),⁶ raises concerns on whether ambulatory care represents a cost-effective intervention in the treatment of primary spontaneous pneumothorax (PSP).

Using the RAMPP trial data, a prospective, within-trial economic analysis was done to determine whether ambulatory management of patients with PSP was cost-effective when compared with standard care.

METHODS

Trial design

Details of the RAMPP trial have been reported in detail elsewhere.⁵ Briefly, RAMPP was a multicentre, open-label, randomised controlled trial comparing ambulatory management of primary pneumothorax with standard care based on national guidelines.⁷

Case definition

ILD and pulmonary sarcoidosis are a composite of chronic respiratory diseases that impair lung function and oxygen uptake through scarring and/or inflammation. The International Classification of Diseases (ICD), 10th revision codes included under this heading are D86-D86.2, D86.9 and J84-J84.9 (box 1), and the ICD, ninth revision codes are 135-135.9, 515 and 515.9-516.9. Notably, the category of ILD and pulmonary sarcoidosis here did not include lung diseases due to external agents, drug-induced interstitial lung disorders, or ILDs due to systemic or rheumatological disease.

Table 1 Baseline characteristics by treatment allocation

	Patients receiving standard care (n=113)	Patients receiving ambulatory care (n=114)
Female	21 (18%)	21 (19%)
Age, years (SD)	30 (9)	31 (8)
Ethnicity		
White	103 (91%)	102 (90%)
Ethnic minority	10 (9%)	11 (10%)
Previous pneumothorax	31 (27%)	24 (21%)
Tobacco smoking status*		
Never smoked	36 (32%)	35 (32%)
Ex-smoker	24 (21%)	18 (16%)
Current smoker	53 (47%)	57 (52%)
Marijuana smoking status†		
Never smoked	54 (49%)	57 (52%)
Ex-smoker	27 (25%)	19 (17%)
Current smoker	29 (26%)	33 (30%)

Data reported as responses/denominator (%), except age which was reported as mean (SD).
 *Missing: ambulatory care n=4.
 †Missing: standard care n=3; ambulatory care n=5.

Participants

Eligible patients had presented with a symptomatic spontaneous pneumothorax (confirmed by a chest radiograph or CT scan) and were aged 16–55 years. Patients requiring intervention could be enrolled and randomly assigned up to 24 hours after presentation, provided that they remained hospitalised with an ongoing symptomatic pneumothorax despite initial intervention (eg, patients treated initially with aspiration and observed overnight) requiring chest tube insertion.

Interventions

Patients were randomly assigned (1:1) to either insertion of an ambulatory device (Rocket Pleural Vent, Rocket Medical, UK) or standard care (aspiration, standard chest tube insertion or both). All patients were followed up at 1 week after the completion of treatment and 30 days, 6 months and 12 months after randomisation. Hospital admissions and pneumothorax recurrence were measured at each follow-up point. Data were collected on further hospital admissions, wider healthcare resource use, pain and breathlessness Visual Analogue Scale (VAS) scores, quality of life, days off work (if applicable) and smoking status. Patients who were not able to attend face-to-face follow-up appointments were contacted by telephone to

check for complications or recurrence, and if this was not possible, data on recurrence were collected through hospital medical records.

Follow-up and outcomes

The primary outcome used in the trial was the total length of hospital stay up to 30 days after randomisation, including initial hospital stay and readmissions.⁵ For this analysis, the perspective adopted in the economic evaluation was that of the National Health Service (NHS). We included the costs associated with the following healthcare resource use categories from randomisation to 12-month follow-up:

- ▶ Initial procedures for the treatment of spontaneous pneumothorax (including insertion of an ambulatory device, aspiration, standard chest tube insertion or a combination of the latter two).
- ▶ Initial length of stay following spontaneous pneumothorax.
- ▶ Subsequent procedures for pneumothorax.
- ▶ Subsequent stays in hospital or day cases due to any reason.
- ▶ Accident and emergency visits.
- ▶ Secondary outpatient care visits.
- ▶ Primary care visits, including visits to a general practitioner (GP) at home, doctor's office or via telephone or to nurse.
- ▶ Visits for physiotherapy.

Costs of performing the initial procedures to treat pneumothorax were obtained through a micro-costing study in which a number of interventions performed in RAMPP were observed. Staff time included the consultant physician, specialist registrar, nurse and healthcare assistant and was valued using average salaries for that position.⁸ Unit costs of disposables were valued using prices obtained from the NHS Supply Chain.⁶ Costs of medications and sedation drugs were obtained from the British National Formulary (<https://bnf.nice.org.uk/>). Finally, costs of investigations undertaken as part of the intervention, including chest X-rays, were obtained from NHS reference costs.⁹

All other follow-up resource use was collected using patient questionnaires administered at treatment completion, 1, 6 and 12 months. As an aide memoire, patients were also provided with a resource-use log designed for them to fill in every time they had a contact with the healthcare system. Unit costs for consultations with GPs and nurses were obtained from the Personal Social Services Research Unit's Unit Costs of Health and Social Care publications for 2019.⁸ For all other contacts, unit costs were derived from the NHS National Schedule of Reference Costs 2018/19.⁸ Using the reasons for hospitalisation reported by patients in the resource-use questionnaires, we obtained diagnosis and procedure codes. These were then translated into a Healthcare Resource Group (HRG) using the HRG4+ 2018/19 Reference Costs Grouper (NHS Digital). Each HRG was then linked to a series of elective, non-elective and day-case reference costs obtained from the 2018/19 schedule of reference costs. All costs are reported in 2019 prices.

Table 2 EQ-5D utility and EQ-VAS scores at follow-up by treatment allocation

	Patients receiving standard care	Patients receiving ambulatory care	Mean difference (95% CI)	P> z
EQ-5D utilities (SD)				
Baseline	0.57 (0.24), n=110	0.57 (0.26), n=109	−0.01 (−0.07 to 0.06)	0.86
Treatment completion	0.75 (0.19), n=60	0.76 (0.17), n=76	0.01 (−0.05 to 0.07)	0.65
1 week	0.83 (0.17), n=97	0.86 (0.12), n=90	0.03 (−0.01 to 0.07)	0.15
1 month	0.87 (0.16), n=88	0.89 (0.12), n=87	0.02 (−0.02 to 0.07)	0.29
6 months	0.91 (0.12), n=70	0.87 (0.23), n=73	−0.03 (−0.09 to 0.03)	0.30
12 months	0.92 (0.12), n=54	0.93 (0.10), n=55	0.01 (−0.03 to 0.05)	0.60
EQ-VAS scores (SD)				
Baseline	60 (23), n=110	56 (21), n=109	−3 (−9 to 2)	0.25
Treatment completion	78 (15), n=60	75 (19), n=76	−3 (−9 to 2)	0.26
1 week	84 (14), n=97	84 (13), n=90	0 (−4 to 4)	0.84
1 month	85 (17), n=88	88 (11), n=86	4 (−1 to 8)	0.10
6 months	89 (14), n=70	88 (11), n=73	−1 (−5 to 3)	0.65
12 months	94 (7), n=54	91 (9), n=55	−3 (−6 to 0)	0.06

EQ-5D, EuroQol-5 Dimensions-5; VAS, Visual Analogue Scale.

Table 3 Twelve-month mean healthcare resource use (SD) by treatment allocation in the available case analysis

	Patients receiving standard care	Patients receiving ambulatory care	Mean difference (95% CI)	P> z
Initial length of stay, days	4.1 (4.9)	1.3 (3.2)	-2.8 (-3.8 to -1.7)	<0.0001
Hospital days due to readmissions at 1 month	1.1 (3.0)	0.8 (2.5)	-0.3 (-1.0 to 0.5)	0.49
Hospital days due to subsequent admissions	1.6 (4.7)	1.8 (8.7)	0.3 (-1.3 to 2.3)	0.77
Primary care visits				
General practice surgery	1.3 (2.6)	1.2 (2.3)	-0.1 (-0.8 to 0.5)	0.70
Home	0	0	0	n/a
Telephone	0.1 (0.4)	0.2 (0.7)	0.1 (-0.0 to 0.2)	0.24
Outpatient visits	1.7 (3.0)	2.6 (2.8)	1.0 (0.2 to 1.7)	0.012
Outpatient transport, rides	0	0.0 (0.3)	0.0 (0.0 to 0.1)	0.18
Accident and emergency visits	0.8 (1.4)	0.8 (1.1)	0 (-0.3 to 0.3)	0.98
Ambulance use, rides	0.1 (0.3)	0.1 (0.3)	-0.0 (-0.1 to 0.1)	0.75
Practice nurse visits	0.5 (2.1)	0.2 (0.8)	-0.3 (-0.8 to 0.1)	0.17
Physiotherapy visits	0.3 (1.7)	0.1 (0.7)	-0.2 (-0.6 to 0.1)	0.26

Although not relevant to the NHS perspective adopted, additional analyses was performed including the amount of days off work (if applicable) that patients had to take during the 12-month follow-up. Days off work was valued using UK mean earnings.¹⁰

Generic health-related quality of life (HRQoL) was measured using the EuroQol-5 Dimensions-5 Levels (EQ-5D-5L) questionnaire and EQ-VAS at time of randomisation (ie, baseline) and at each follow-up point.¹¹ EQ-5D-5L responses were converted into utilities using the validated mapping function to derive utility values for the EQ-5D-5L from the existing EQ-5D-3L version.¹²

Statistical analysis

Utility and VAS scores at each follow-up point were presented as means (SD). A quality-adjusted survival curve was generated by plotting, against time, the product of the mean utility of patients

living at time *t* and the probability of surviving to time *t*, in this case 1 as no deaths were observed during 12-month follow-up, in order to create three periods (ie, randomisation to 1-month follow-up, 1–6-month follow-up and 6–12-month follow-up). The area under this quality-adjusted survival curve then gave the mean quality-adjusted survival in each treatment group or quality-adjusted life-years (QALYs) gained over the 12-month follow-up. Utility was assumed to change linearly between each follow-up, rather than changing at the mid-point between follow-ups or being maintained from one follow-up to another.

For the base case, given we had missing data for follow-up resource use and EQ-5D responses, multiple imputation was used to impute missing cost and utility values (please see online supplemental table1).^{13–15} As per recommended best practice, imputation was implemented separately by randomised treatment allocation.¹⁶ Costs were imputed at the most disaggregated level at which the model would converge. As a result, we imputed values for general practice consultation costs (at practice, home and telephone); hospitalisation readmission costs; outpatient care costs (outpatient visits and transportation to visits); emergency care costs (visits to emergency departments and transport by ambulance) and other healthcare costs (physiotherapy and nurse visits). There were no missing data for treatment and initial hospitalisation costs. Rather than imputing missing responses for each of the five domains in the EQ-5D-5L, we imputed the overall EQ-5D-5L utility.¹⁷ The imputation of costs and utility was conducted using predictive mean matching (ie, imputes data from similar patients with complete data). Imputation was conducted using age, sex, ethnicity, tobacco and marijuana use history, history of pneumothorax and pneumothorax recurrence. We generated 40 replacement values for each missing case, generating 40 imputed data sets using the Stata 'mi estimate' command. We obtained mean estimates of cost and utility and SD. Differences across patients groups were obtained using ordinary least squares regression using the 'mi estimate: reg' command.

In a sensitivity analysis, we also performed an available case analysis. For each treatment group, average resource use/costs were summed over the follow-up periods. Results are then presented as means together with 95% CIs, generated through 10 000 bootstrap estimates. Mean differences in QALYs, resource use and costs between the two treatment groups were also estimated, as well as the 95% CI of the difference using bootstrapping.

Cost-effectiveness was assessed through estimation of the incremental cost per QALY gained. This is based on the difference in mean total cost per patient between the intervention and control group (ambulatory and standard care, respectively), divided by the difference in mean QALYs in the two groups. The resulting incremental cost-effectiveness ratio (ICER) was compared with reference to what the NHS is willing to pay (WTP) for an additional QALY; this currently being ≤£20 000 per QALY gained.¹⁸ Results based on the 10 000 bootstrap replications of QALYs and total care costs at 12 months

Table 4 One-year mean cost differences between patients randomised to standard care and ambulatory care

	Difference Mean (95% CI)	P> z
Base case: multiple imputation		
Initial admission	-£1035 (-1490 to -578)	<0.001
Treatment	£158 (134 to 179)	<0.001
Readmissions at 1 month	-£147 (-454 to 141)	0.34
Subsequent admissions	£61 (-444 to 567)	0.81
Primary care	£1 (-20 to 22)	0.94
Outpatient care	£188 (91 to 285)	<0.001
Emergency care	10 (-47 to 67)	0.74
Other health	-9 (-22 to 4)	0.18
Total NHS	-£788 (-1527 to -50)	0.037
Productivity losses	101 (-1625 to 1826)	0.91
Total costs	-688 (-2688 to 1312)	0.50
Sensitivity analysis: available case		
Initial admission	-£1036 (-1487 to -583)	<0.001
Treatment	£157 (135 to 179)	<0.001
Readmissions at 1 month	-£143 (-456 to 162)	0.36
Subsequent admissions	£120 (-468 to 718)	0.70
Primary care	-£3 (-29 to 24)	0.86
Outpatient care	£140 (30 to 248)	0.012
Emergency care	-£4 (-70 to 58)	0.90
Other health	-£15 (-37 to 2)	0.14
Total NHS	-£782 (-1550 to -4)	0.049
Productivity losses	£325 (-1857 to 3272)	0.80
Total costs	-£456 (-2995 to 2644)	0.76

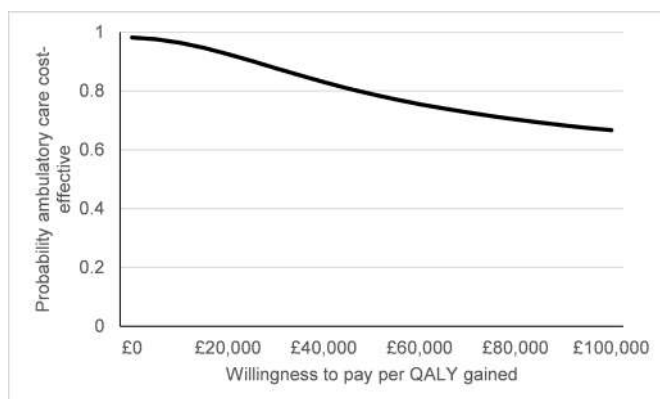


Figure 1 Cost-effectiveness acceptability curve—probability that ambulatory care was cost-effective when compared standard care after multiple imputation analysis. QALY, quality-adjusted life-year.

are displayed on a cost-effectiveness plane. The cost-effectiveness plane is used to visually represent the differences in costs and health outcomes between the two study groups in two dimensions. A cost-effectiveness acceptability curve was drawn to represent the probability of cost-effectiveness for different values of WTP.¹⁹ Subgroup cost-effectiveness analysis was done for previous pneumothorax.¹

All analyses were performed using STATA MP V.15 (64-bit). Statistical significance was set at $p < 0.05$.

RESULTS

Study participants

We recruited patients between 27 August 2015 and 12 March 2019, reaching our target of 236 participants, of whom 117 were assigned to ambulatory care and 119 to standard care. For the primary outcome, we analysed 114 (97%) of 117 patients who received ambulatory care and 113 (95%) of 119 who received standard care, because data were not available for the remaining patients. These patients then formed the basis of the cost-effectiveness analysis (table 1).

Quality of life

Responses to the EQ-5D-5L at baseline, treatment completion, 1 week and 1, 6 and 12 months, as well as numbers responding, are reported in online supplemental tables 2 and 3. We found that patients attending their 12-month follow-up were more likely to be female and have no history of smoking tobacco or marijuana (online supplemental table 4), but these did not differ by treatment group (online supplemental table 5). EQ-5D responses were then converted into utilities (table 2). There were no statistically significant differences in utilities or VAS scores at 1 week and 1, 6 and 12 months.

Given there were no observed deaths, follow-up duration (ie, 12 months) was combined with EQ-5D-5L utilities to estimate QALYs at 12 months after randomisation. After imputing for

missing EQ-5D data, patients receiving ambulatory care had a non-significant decrease of 0.001 (95% CI difference: -0.032 to 0.030) QALYs when compared with those receiving standard care. In the available case analysis, ambulatory care patients also had a non-significant decrease of 0.005 (95% CI difference: -0.037 to 0.025).

Resource use and costs

For patients receiving ambulatory care, the initial mean hospital stay was of 1.33 (SD 3.24) days compared with 4.11 (SD 4.91) days in the standard care group, a statistically significant reduction of 2.78 (95% CI: -3.87 to -1.69 ; $p < 0.0001$) days in hospital. There were no statistically significant differences between the two groups in hospital days due to readmissions up to the 1-month follow-up, with patients receiving ambulatory care having stays in hospital due to readmissions of 0.81 (SD 2.49) days versus 1.06 (SD 3.04) days in the standard care group ($p = 0.49$). Except for outpatient visits, where patients receiving ambulatory care had, on average, 0.98 (95% CI difference: 0.21 to 1.71 ; $p = 0.012$) more visits than those receiving standard care over the course of 1 year, there were no other statistically significant differences in healthcare resource use (table 3). Resource use by follow-up, as well the number of patients for whom we had data for, is reported in online supplemental table 6.

There were no missing data regarding the costs of initial hospital stays, trial treatments and 1-month readmissions. Given the significant reduction in initial hospital stay, mean costs of the initial hospital stay were significantly lower in the ambulatory care group than the standard care group ($-\text{£}1036$, 95% CI difference: -1487 to -583 , $p < 0.0001$ – table 4). However, costs of pneumothorax treatment were significantly higher for the ambulatory care group ($\text{£}329$) than the standard care group ($\text{£}172$; $p < 0.0001$). There were no significant differences in 1-month readmissions or subsequent hospital admissions over the 1 year of follow-up. For follow-up costs, results of the multiple imputation showed that, except for outpatient care costs, which were higher in the ambulatory care group ($\text{£}188$, 95% CI difference: 91 to 285 , $p < 0.001$), there were no other significant differences in cost categories (table 4). Overall, during the 1-year follow-up, patients in the ambulatory care group had significantly lower NHS healthcare costs than those in the standard care group ($-\text{£}788$, 95% CI difference: -1527 to -50 , $p = 0.037$). Online supplemental figure 1 presents how mean QALY and cost differences between the two patient groups varied across the 40 imputed datasets used in the multiple imputation analysis.

Over the 12 months, mean number of days off work was 26 in patients receiving ambulatory care compared with 24 in those receiving standard care, a non-significant increase of 2 (95% CI difference: -14 to 25 ; $p = 0.81$) days. This resulted in non-significantly higher productivity losses in the ambulatory care group (table 4). Overall, when NHS and productivity losses were combined together, there were no overall significant differences across groups.

Cost-effectiveness

Cost-effectiveness was assessed using an NHS perspective. Given that standard care resulted in non-significantly higher QALYs and significantly higher NHS costs than ambulatory care, cost-effectiveness was assessed by comparing the additional costs of standard care versus ambulatory care, divided by the additional QALY gains when standard care was compared with ambulatory care.

In the multiple imputation analysis, the incremental cost per QALY gained when standard care was compared with ambulatory care was $\text{£}799\,066$, well above the current $\text{£}20\,000$ cost-effectiveness threshold. At this cost-effectiveness threshold, the average, across the 40 imputed datasets, probability that ambulatory care was cost-effective over standard care was 0.93 (figure 1). Across the 40 imputed datasets this probability ranged between 0.71 and 0.99 (online supplemental figure 2). Repeating the analysis, using a wider perspective (ie, including NHS costs and productivity losses), the ICER when standard care was compared with ambulatory care was $\text{£}696\,986$ per QALY gained, again above current thresholds of cost-effectiveness. From an NHS perspective, results of the available case analysis showed that the ICER of standard care versus ambulatory care was $\text{£}151\,438$ (table 4, online

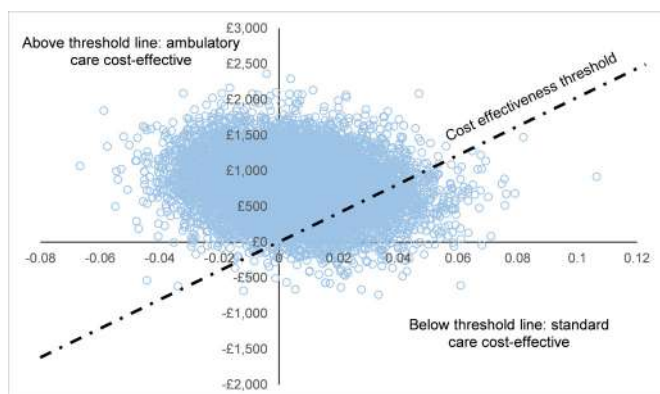


Figure 2 Cost-effectiveness plane—cost-effectiveness of standard care when compared with ambulatory care in the available case analysis y-axis: Incremental costs when standard care was compared with ambulatory care x-axis: Incremental quality-adjusted life-years when standard care was compared with ambulatory care.

supplemental table 7, well above conventional thresholds of cost-effectiveness, with the probability that ambulatory care was cost-effective at a £20 000 per QALY threshold being 0.87 (figure 2). From a wider perspective, the ICER was £89 904 per QALY gained when standard care was compared with ambulatory care.

When the multiple imputation analysis was restricted to patients with previous history of pneumothorax, patients receiving ambulatory care had significantly lower NHS costs than those receiving standard care (−£1960, 95% CI difference: −3267 to −654) and non-significantly lower QALYS (−0.010, 95% CI difference: −0.070 to 0.051). In this subgroup, therefore, the incremental cost per QALY gained when standard care was compared with ambulatory care was £201 140.

DISCUSSION

This multicentre, open-label, randomised controlled trial assessed the cost-effectiveness of an ambulatory treatment strategy for PSP with standard care using evidence-based guidelines (aspiration, chest drain insertion or both). The results show the cost-efficiency of the ambulatory strategy, resulting in significantly lower NHS costs during the 1 year of follow-up, with no difference in health outcome.

Given that the difference in QALYs between the two study groups was very small and non-significant, our results of cost-effectiveness were driven by differences in cost. We found that the additional cost per QALY gained when standard care was compared with ambulatory care was £799 066 after imputing for missing data. This high ICER, which is well above current UK cost-effectiveness thresholds, was obtained by dividing the difference in costs (standard care generated significant additional costs per patient when compared with ambulatory care) by the very small difference in QALYs.

Serious adverse events, defined as those needing admission to hospital, occurred exclusively in the ambulatory care arm.¹ Serious adverse events related to treatment included enlargement of pneumothorax despite the ambulatory device being in place and device blockage and kinking, requiring chest tube insertion and hospitalisation. In the ambulatory care group, three patients had unrecognised haemopneumothoraces, which at review were not considered related to the intervention. Although this higher rate of serious adverse events is clearly important, it did not translate into higher costs of hospital readmissions in the ambulatory care group or negative health outcomes, as QALY gains were similar in both treatment groups.

Despite patients in the ambulatory care group spending significantly less time in hospital than those receiving standard care, we saw no differences, over the course of the year, in the number of days patients had to take off work. Although patients with primary pneumothorax being relatively young and otherwise healthy, on average, over the course of the year following pneumothorax, patients lost approximately 25 days off work, considerably more than the average 4.68 days lost due to sickness per employee in the UK.²⁰

The burden of pneumothorax on patients was also observed in low levels of self-reported HRQoL in patients, particularly at time of pneumothorax and shortly after. At time of randomisation, patients reported utilities of 0.57 (out of a maximum of 1), with 59% reporting moderate to extreme pain. However, by end of follow-up mean EQ-5D utility was 0.92, with 62% of patients reporting perfect health. Our results also show that most of the care for pneumothorax at follow-up was in hospital. For example, irrespective of treatment group, patients made less than 1.5 visits to their GP over the course of the year. In addition, virtually all (98%) the NHS costs incurred over 1-year follow-up were incurred in hospital (treatment, hospitalisations, outpatient specialist care and emergency care).

Limitations

In addition to the trial limitations already reported,¹ this economic evaluation alongside RAMPP also had some shortcomings. First, despite best efforts, we had considerable missing quality of life and resource use data at the latter follow-ups, especially at the 1-year follow-up. Patients who suffer with PSP are usually young with minimal comorbidity, and after resolution of their pneumothorax, their quality of life quickly returns to pre-morbid levels (see high EQ-5D scores at follow-up). As such, we presume that they no longer feel the need to attend follow-up, even as part of a clinical

trial. This missing data can not only lead to loss of statistical power but also to bias.²¹ We, therefore, used multiple-imputation methods. Both after multiple imputation and when using available information only, we found that our conclusions that ambulatory care was cost-effective remained unaltered. If anything, the likelihood of ambulatory care being cost-effective was increased.

Quality of life was assessed at defined fixed time points over follow-up, rather than regularly (eg, weekly), or when an adverse or subsequent event occurred. As a result, the true impact of the interventions on quality of life might not have been captured in full. For example, the benefits of shorter admissions might not have been captured. Equally, the impact of adverse events or subsequent pneumothoraces happening half-way through follow-up might not have been captured at the follow-up visit. Therefore, the impact of an adverse event, whose consequences could last for a number of days and result in a reduction in quality of life during that time, but had resolved at the time of the follow-up visit would not have been captured.

In a bid to avoid patient overburden, follow-up questionnaires were kept to a minimum. As a result we did not include questions on informal care, more in depth questions about return to work and other NHS resource use.

There was a slight difference in proportion of patients with previous pneumothorax between the two groups. However, in this pragmatic study, this information would not have impacted on the initial treatment options for the patients assessed by the primary outcome. In the longer term, the patients with recurrent episodes may have been more likely to be referred for elective thoracic surgery (for recurrence prevention). However, the authors' feel that this would not have a significant impact on the health economic (HE) analysis.

In conclusion, in patients with PSP, ambulatory management not only reduces initial hospital stay but also overall NHS costs over 12-month follow-up, with no decrease in health outcomes as measured by quality of life. Outpatient ambulatory management is highly likely to be a cost-effective option in the management of this condition.

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Contributors RH and NMR conceived study design, trial management and oversight, patient recruitment and data collection. RL-F and FL: statistical analysis. RL-F: literature search and initial manuscript preparation. RL-F is the guarantor of the data. All authors reviewed and approved the final manuscript.

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Competing interests NMR reports consultancy fees from Rocket Medical, during the conduct of the study, and Lung Therapeutics and grants from BD Biosciences, outside the submitted work. All other authors declare no competing interests.

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Construção de um programa de ventilação ao domicílio: população, equipamento, entrega e custo

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RESUMO

A ventilação mecânica no domicílio (VMD) melhora a qualidade de vida e de sobrevivência em pacientes com doenças neuromusculares (DNM). Os países em desenvolvimento podem beneficiar da evidência publicada relativamente à prevalência, custo do equipamento, questões técnicas e organização da VMD na DNM, facilitando o desenvolvimento de programas locais de VMD chave-na-mão. Infelizmente, esta evidência está dispersa na literatura existente. Pesquisamos na Medline por publicações em inglês e francês entre 2005 e 2020. Esta revisão narrativa analisa 24 programas internacionais de VMD. A prevalência estimada (min- max) de VMD é de $\pm 7.3/100\,000$ habitantes (1.2-47), com todas as doenças combinadas. A prevalência da VMD está associada ao produto interno bruto per capita nestes 24 países. A prevalência de DNM é de cerca de 30/100 000 habitantes, dos quais $\pm 10\%$ usariam VMD. A ventilação noturna (8/24 horas), descontínua (8-16/24 horas) e contínua ($>16/24$ horas) é suscetível de afetar cerca de 60%, 20% e 20% dos pacientes com DNM que usam VMD. Um orçamento mínimo de cerca de 168 euros/paciente/ano (504 euros/100 000 habitantes), incluindo apenas o custo do equipamento, deve cobrir o custo do equipamento de VMD em países de baixos rendimentos. Ao incluir serviços e manutenção, o orçamento pode aumentar drasticamente até entre 3232 e 5760 euros/paciente/ano. A emergência de programas de VMD em países em desenvolvimento revela o impacto positivo da cooperação internacional. Atualmente, pelo menos 12 novos países de rendimento médio e baixo estão a desenvolver programas de VMD. Esta revisão com dados atualizados sobre a prevalência, questões técnicas, custo do equipamento e serviços para a VMD deve estimular diálogos objetivos entre as partes interessadas (associações de pacientes, profissionais de saúde e políticos); potencialmente conduzir à produção de estratégias viáveis para o desenvolvimento de VMD em casos de pacientes com DNM que vivem em países em desenvolvimento.

INTRODUCTION

Hypercapnic respiratory failure due to alveolar hypoventilation is a common complication of severe neuromuscular disorders (NMD), obesity hypoventilation syndromes (OHS), chronic obstructive pulmonary diseases (COPD) and restrictive thoracic diseases (RTD).¹ Home mechanical ventilation (HMV) is effective treating chronic hypercapnic respiratory failure in the long term.² HMV via positive pressure was introduced in the 1980s, initially for patients with poliomyelitis, NMD and RTD.³ There is accumulating evidence supporting improvement of gas exchange, quality of life and prolongation of survival by HMV in patients with hypercapnic respiratory failure.⁴ In 2005, the estimated prevalence of HMV in Europe was 6.6 per 100 000 people.⁵ To date, little is known regarding the use of HMV in developing countries.

Developing countries interested in using HMV may benefit from published evidence regarding the organisation of HMV. They should be aware

of which patients are eligible for HMV and understand: number, type, cost of equipment needed for HMV and which ventilation approach is desired.⁶ Unfortunately, such information is scattered in the existing medical literature. The present authors suggest that collating the above-mentioned information is likely to facilitate the development of local turn-key HMV programmes.

This review discusses basic evidence with regards to HMV, with a focus on patients affected by NMD. Basic evidence includes the prevalence of disorders eligible for HMV, the prevalence of both HMV in general and within disorders and the technicalities and cost of equipment for HMV. This review also provides an original algorithm to calculate the cost of HMV equipment in accordance with local financial resources. This review aims to provide consistent evidence about existing HMV programmes, which will trigger an ongoing dialogue between patient associations, healthcare professionals and politicians. Informed dialogue should help to develop a workable strategy for the development of HMV in patients with NMD living in developing countries.

PREVALENCE

A search of Medline/PubMed for HMV articles published between 2005 and 2020 was performed. The search items included: neuromuscular diseases, HMV, domiciliary ventilation, prolonged ventilation, long-term ventilation and non-invasive ventilation.⁷ To determine the prevalence of HMV, we selected original articles that included comprehensive national or regional data on HMV. We excluded studies on any or all of the following: reporting the use of continuous positive airway pressure (CPAP) devices or mixing data from CPAP and assisted ventilation, using HMV in the hospital, conducted in a single centre, selecting a limited number of disorders, covering a limited range of age of HMV users or reporting the use of invasive techniques solely. Prevalence data were standardised by 100 000 inhabitants.

Prevalence of NMDs

The development of HMV programmes presupposes the identification of disorders potentially eligible for HMV initiation. Eligible disorders for HMV are classically categorised in four groups: NMD, OHS, COPD and RTD.⁸

NMD include amyotrophic lateral sclerosis, bilateral diaphragm paralysis, post-polio syndrome, spinal muscular atrophies, type 1 myotonic dystrophy, myopathies, muscular dystrophies, chronic polyradiculoneuritis and multiple sclerosis.⁸ Although the incidence of patients with NMD is stable, the prevalence rises slightly due to improved outcomes in this patient group.^{9,10} In France (2012), the number of people affected by NMD was estimated to be between 20 and 25 000 cases for 65.5 million inhabitants, corresponding to a prevalence of about 30/100 000 inhabitants.⁸



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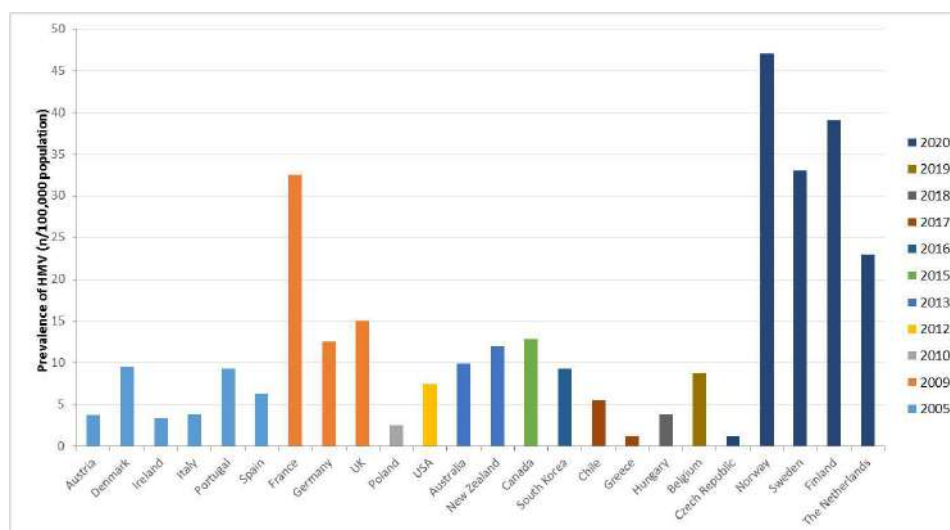


Figure 1 Most recently estimated national prevalence of HMV in 24 countries. Prevalence by date of published reference: Austria,⁵ Denmark,⁵ Ireland,⁵ Italy,⁵ Portugal,⁵ Spain,⁵ France,⁶ Germany,⁶ UK,⁶ Poland,¹¹ USA,¹² Australia,¹³ New Zealand,¹³ Canada,¹⁴ South Korea,¹⁵ Chile,¹⁶ Greece,¹⁷ Hungary,¹⁸ Belgium,¹⁹ Czech Republic,⁹ Norway,²⁰ Sweden,²⁰ Finland,²⁰ Netherlands.²¹ HMV, home mechanical ventilation.

Prevalence of HMV

The largest survey describing the use of HMV was conducted by Lloyd-Owen *et al.*⁵ The estimated prevalence of HMV in East European countries, all disorders combined, was as low as 0.1 per 100 000 inhabitants as compared with 6.6 in Western and Central European countries.⁵

Figure 1 depicts the most recently reported prevalence from 24 national HMV programmes between 2005 and 2020.^{5 6 9 11–21} Available prevalence, ranging 1.2–47/100 000 inhabitants, was highly variable across countries. Northern European countries reported the most recently published and highest prevalence of HMV.

Large differences are reported across regions within the same country, despite a homogeneous national healthcare system and similar indications for treatment.²² For example, the prevalence of HMV varies between 1.2 and 4.0 among 16 regions in Poland,²³ between 4.5 and 13.0 among eight states and territories in Australia¹³ and between 0.4 and 15.5 among nine territories in Canada.¹⁴ Different reasons can explain such large variations within countries. Garner *et al* found that HMV prescribing patterns depend on each centre's location, size and experience. They found that the more densely populated Australian states have the highest prevalence of HMV.¹³ Dybwick *et al* found that an uneven distribution of the 'enthusiasm' among hospitals was a major factor impacting the geographical distribution of HMV in Norway.²⁴ This finding from a high-income country suggests that the access to HMV would not solely be affected by objective parameters such as the level of healthcare development. Subjective aspects such as the variable interest of professionals and bureaucrats in specific healthcare domains may play a significant role in the local development of HMV.

Consideration of the maximal number of eligible HMV users contributes to the prognostication of the costs of HMV in a well-defined patient group. Table 1 presents data from comprehensive surveys between 2004 and 2019. Surveys were included, provided they reported nationwide prevalence of HMV in the main diagnostics eligible for HMV. Table 1 includes 35 413 HMV users, followed up by 578 centres from 22 countries representing 546 million inhabitants. Table 1 provides a large and novel view regarding HMV users worldwide. It suggests a mean prevalence of HMV at 7.3/100 000 inhabitants, which is likely to be underestimated.

Table 1 suggests an uneven distribution of prevalence of HMV by disorders among countries. Variable expertise in the care of disorders eligible for HMV, combined with variable systems of reimbursement, may be an explanation in some countries with national policies dictating which users are ventilated.

Prevalence of HMV in NMDs

As previously stated, the prevalence of HMV in NMDs is reported as stable or slowly increasing over time. Table 1 reports a prevalence of NMDs using HMV at 2.9/100 000 inhabitants, which is in line with France in 2013 (3/100 000),⁸ and Belgium in 2019 (2.6/100 000).¹⁹ Current prevalence data suggest that about 10% of all NMDs would use HMV.

Today, the reimbursement of HMV in NMDs is consistent across West-Europe but varies widely in other areas. Central Europe is a good example. In 2008, the National Health Authorities in Serbia recommended full reimbursement of respiratory equipment for NMDs.²⁵ According to the information from the Russian Duchenne (<https://dmd-russia.ru>) and spinal muscular atrophy (www.f-sma.ru) websites, as much as 20% DMD and 8% SMA patients would use HMV in Russia. Reimbursement policies may be totally lacking in countries neighbouring Russia such as Ukraine, where the prevalence of Duchenne patients receiving HMV is estimated to be as low as 0.2% of all patients with DMD (<http://dmd.org.ua/>).

Prevalence of HMV according to nation wealth

It can be hypothesised that the development of HMV correlates with the economic development of a given country. Figures 2 and 3 present the correlation between the prevalence of HMV and markers of both wealth and development of countries, such as the gross domestic product (GDP, figure 2) and the human development index (HDI, figure 3). The GDP is the monetary value of all finished goods and services produced in a country. GDP is considered as a key tool to guide policymakers in strategic decision-making. The HDI, from 0 to 100 points, assesses the development of a country through three dimensions: the life expectancy, the level of education and the standard of living. Values of GDP and HDI were collected using the Development Programme of the United Nations.²⁶ Values of GDP and HDI reported in figures 2 and 3 correspond to the year of reported prevalence of HMV in 24 countries.

Box 1

In 2005, the prevalence of home mechanical ventilation (HMV) in Europe was 6.6/100 000 inhabitants.

According to international HMV programmes (figure 1, data from 24 countries), the prevalence of HMV ranges 1.2–47/100 000 inhabitants.

The prevalence of HMV varies between different regions of the same countries despite a homogeneous healthcare system. Uneven distribution of the 'enthusiasm' between hospitals impacts the distribution of HMV.

Table 1 Prevalence of HMV/100,000 population, by diagnostic, in 22 countries

Country	Date	HMV					Diagnosis (% cases)				Prevalence by diagnosis			
		People	Prevalence	Cases	Centres	Area	NMD	OHS	RTD	COPD	NMD	OHS	RTD	COPD
		million	n/100.000	n	n	Type	%	%	%	%	n	n	n	n
Sweden	2004	9	10,4	1100	35	Nation	27	NA	13	5	2,8	NA	1,4	0,5
Austria	2005	8,9	3,8	508	7	Nation	25	NA	26	49	1,0	NA	1,0	1,9
Belgium	2005	10,3	5	501	17	Nation	52	NA	29	19	2,6	NA	1,5	1,0
Denmark	2005	5,4	9,6	503	2	Nation	86	NA	9	5	8,3	NA	0,9	0,5
Finland	2005	5,2	8,7	121	16	Nation	63	NA	20	17	5,5	NA	1,7	1,5
France	2005	61,4	17	6338	58	Nation	24	NA	33	43	4,1	NA	5,6	7,3
Germany	2005	82,4	6,5	4220	22	Nation	27	NA	31	42	1,8	NA	2,0	2,7
Greece	2005	10,9	0,6	122	5	Nation	27	NA	39	34	0,2	NA	0,2	0,2
Italy	2005	57	3,9	1928	44	Nation	24	NA	23	53	0,9	NA	0,9	2,1
Netherlands	2005	16	5,6	918	9	Nation	69	NA	17	14	3,9	NA	1,0	0,8
Ireland	2005	5,1	3,4	157	14	Nation	26	NA	33	41	0,9	NA	1,1	1,4
Portugal	2005	10,4	9,3	801	20	Nation	25	NA	25	50	2,3	NA	2,3	4,7
Spain	2005	41	6,3	1400	15	Nation	28	NA	60	12	1,8	NA	3,8	0,8
UK	2005	49,7	4,1	2842	47	Nation	39	NA	35	26	1,6	NA	1,4	1,1
Norway	2005	4,5	7,8	377	17	Nation	71	NA	13	16	5,5	NA	1,0	1,2
USA	2010	6,6	7,3	221	58	State	69	NA	8	23	5,0	NA	0,6	1,7
Australia	2013	23,1	9,9	2400	27	Nation	33	26	11	10	3,3	2,6	1,1	1,0
N Zealand	2013	4,4	12	525	6	Nation	20	54	5	1	2,4	6,5	0,6	0,1
Canada	2015	35,7	12,9	4334	133	Nation	30	12	9	NA	3,9	1,5	1,2	0,0
Poland	2015	38	2,5	928	9	Nation	52	10	4	21	1,3	0,3	0,1	0,5
Hungary	2018	9,7	3,9	384	17	Nation	11	NA	7	20	0,4	0,0	0,3	0,8
South Korea	2019	51,7	9,3	4785	NA	Nation	42	NA	1,2	27,7	3,9	0,0	0,1	2,6
Total		546,4	7,3	35 413	578		–	–	–	–	–	–	–	–
Mean		–	–	–	–	–	39,5	25,5	20,5	25,2	2,9	1,8	1,3	1,6

Data from studies including the national prevalence of HMV in the four main disorders eligible for HMV.

COPD, chronic obstructive pulmonary diseases; NMD, neuromuscular disorders; OHS, obesity hypoventilation syndromes; RTD, restrictive thoracic diseases.

Although, there were positive relationships between both the prevalence of HMV and the GDP per capita ($R^2=0.4359$), and between the prevalence and the HDI ($R^2=0.3475$), the dispersion of the prevalence seems less pronounced in countries with the lowest GDP. This suggests that GDP is not the only determinant of NIV prevalence. This result should, therefore, be interpreted with caution. However, the wealthiest and more developed countries have the highest prevalence of HMV. It is, therefore, not surprising that new HMV programmes currently developing are in high-income countries such as Singapore,²⁷ Taiwan²⁸ and Saudi Arabia.²⁹ Despite the high prevalence of non-invasive ventilation in high-income countries, it should be borne in mind that large disparities in access to care may persist in these countries.

Next to high-income countries, low to middle-income countries (LMICs) with developing healthcare systems have made efforts to develop HMV. In these countries, HMV is often developed in single centres, and studies do not report comprehensive data. These countries were, therefore, not included in figures 2 and 3. By decreasing order of GDP per capita, middle and low-income countries developing HMV include Thailand,³⁰ China,³¹ Brazil,³² Iran,³³ South Africa,³⁴ Tunisia,³⁵ Malaysia,³⁶ Turkey,³⁷ Argentina,³⁸ Serbia,³⁹ India⁴⁰ and Pakistan.⁴¹

Evolution of the prevalence of HMV

Figure 4 illustrates the evolution over time of HMV in 15 areas, where estimates of prevalence of HMV were available at different periods.^{5 6 13 16 17 19–22 42–49} The number of HMV users were constantly rising, with rapid progression in some countries, and slow progression in others. The progression of HMV in high-income industrialised countries is explained by a drastically increasing prevalence and evolving evidence regarding the benefits of HMV in OHS, but even more so in COPD, leading

to a change in the pattern of prescribing of HMV. The populations treated have persistent smoking habits and are ageing, comorbid and frequently obese. The region of Vaud, Switzerland, is an example of this phenomenon, with a prevalence of HMV increased 2.5-fold since 2000, reaching 37.9 per 100 000 inhabitants in 2020.⁴⁴

TECHNICALITIES AND COSTS OF HMV

Technical aspects of HMV

Depending on the time period of ventilator use per 24 hours, three categories of HMV users can be defined: nocturnal (8/24 hour), discontinuous (8–16/24 hours) and continuous (>16/24 hours, life support) ventilation.^{8 50} Those categories include both non-invasive and invasive techniques of HMV. In Hungary⁵⁰, 74% of HMV users receive HMV at night, 15% between 8 hours and 16 hours and 10% use HMV for more than 16/24 hours.⁵⁰ This is in line with Switzerland (2020), where 9% of NMDs use ventilation for more than 16 hours.⁴⁴ In Belgium (2019), 58%, 17% and 25% of NMDs received nocturnal, discontinuous and continuous ventilation, respectively.¹⁹ Based on those results and on the opinion of the current authors, nocturnal, discontinuous and continuous HMV would roughly affect about 60%, 20% and 20% of patients using HMV. Equipment requirements increase according to the dependence on mechanical ventilation. Bilevel devices may not necessarily be equipped with batteries and provide pressure-cycled ventilation solely. They operate via 110–220 volts electricity and are designed for nocturnal use in bed. By contrast, life-support ventilators provide multiple modes of ventilation, such as volume-cycled ventilation, pressure-cycled ventilation or a mix between volume and pressure modes. They are equipped with internal and external batteries, and alarms aiming at providing secure continuous HMV in all circumstances.

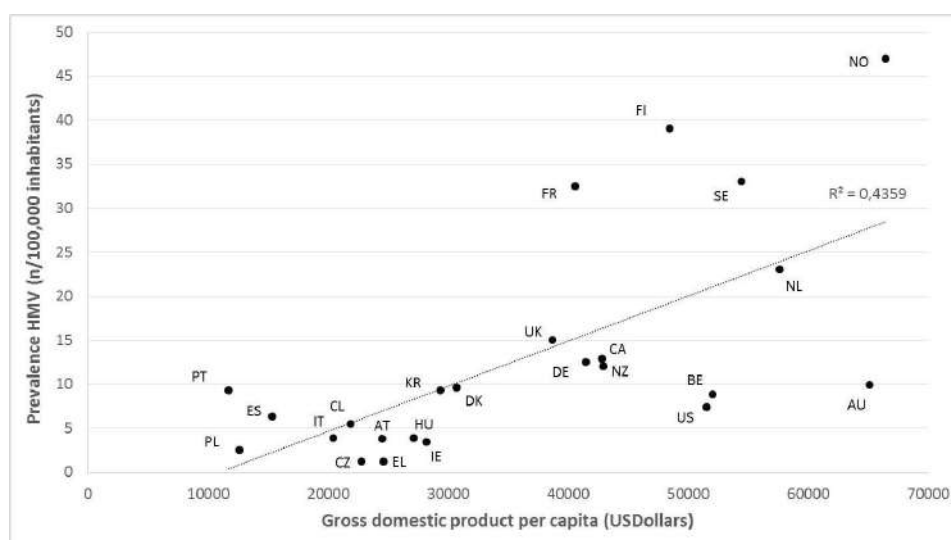


Figure 2 Relationship between the prevalence of home mechanical ventilation (HMV) and the gross domestic product per capita (GDP) in 24 countries. AU, Australia 2013; AT, Austria 2005; BE, Belgium 2019; CA, Canada 2015; CL, Chile 2017; CZ, the Czech Republic 2020; DE, Germany 2009; DK, Denmark 2005; EL, Greece 2017; ES, Spain 2005; FI, Finland 2020; FR, France 2009; HU, Hungary 2018; IE, Ireland 2005; IT, Italy 2005; NL, the Netherlands 2020; NO, Norway 2020; NZ, New Zealand 2013; KR, South Korea 2016; PL, Poland 2010; PT, Portugal 2005; UK, United Kingdom 2009; US, United States of America 2012; SE, Sweden 2020.

Nocturnal ventilation (8 hour)

In this category, patients require ventilation for up to 8/24 hours. The ventilator is used solely at night during sleep. An internal battery is not mandatory, with exceptions for those patients living very far from their reference centre for HMV or living in an environment with inconsistent electrical infrastructure. Bilevel positive airway pressure devices are less expensive than life-support ventilators, and they are effective for nocturnal respiratory support.

Discontinuous ventilation (8–16 hour)

Patients receiving discontinuous ventilation require HMV between 8 hours and 16/24 hours. The ventilator is used at night during sleep, plus a few hours during the daytime. Ventilators, equipped with an internal battery, are ideal but bilevel positive pressure devices can be used. When ventilatory support is used on a wheelchair, the availability of an external battery is desirable.

Continuous ventilation (>16 hour)

In this category, patients need ventilation for more than 16/24 hour. Such patients are at risk of suffocating if mechanical ventilation is interrupted. In this context, patients ideally benefit from two life-support ventilators (or a bilevel at night plus a life-support ventilator for daytime use), equipped with disconnection alarms, an internal battery, and an additional external battery. If no internal battery is available, external supply of electricity is mandatory.

Accessories for HMV

Patients are generally offered HMV *via* non-invasive interfaces such as nasal or oronasal masks. Invasive ventilation is not discussed in this review. The delivery of a circuit and mask two times annually is a minimum—the replaced items can be retained as backup equipment. The provision of a simple resuscitation bag is advisable for each of the three categories, but it is crucial for continuously ventilated patients to ensure ventilatory support in case of ventilator or power failure.⁵¹ The availability of a resuscitation bag also

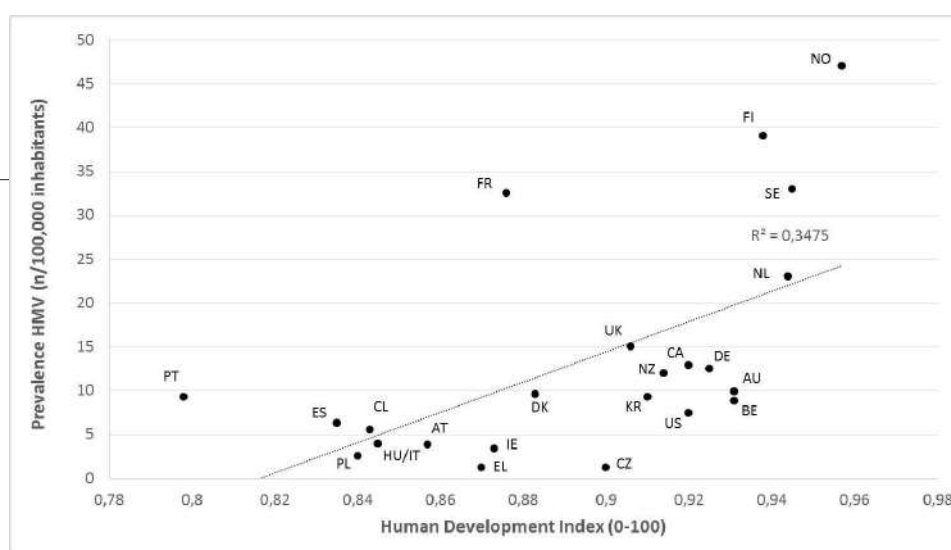


Figure 3 Relationship between the prevalence of home mechanical ventilation (HMV) and the human development index (HDI) in 24 countries. AU, Australia 2013; AT, Austria 2005; BE, Belgium 2019; CA, Canada 2015; CL, Chile 2017; CZ, the Czech Republic 2020; DE, Germany 2009; DK, Denmark 2005; EL, Greece 2017; ES, Spain 2005; FI, Finland 2020; FR, France 2009; HU, Hungary 2018; IE, Ireland 2005; IT, Italy 2005; NL, the Netherlands 2020; NO, Norway 2020; NZ, New Zealand 2013; KR, South Korea 2016; PL, Poland 2010; PT, Portugal 2005; UK, United Kingdom 2009; US, United States of America 2012; SE, Sweden 2020.

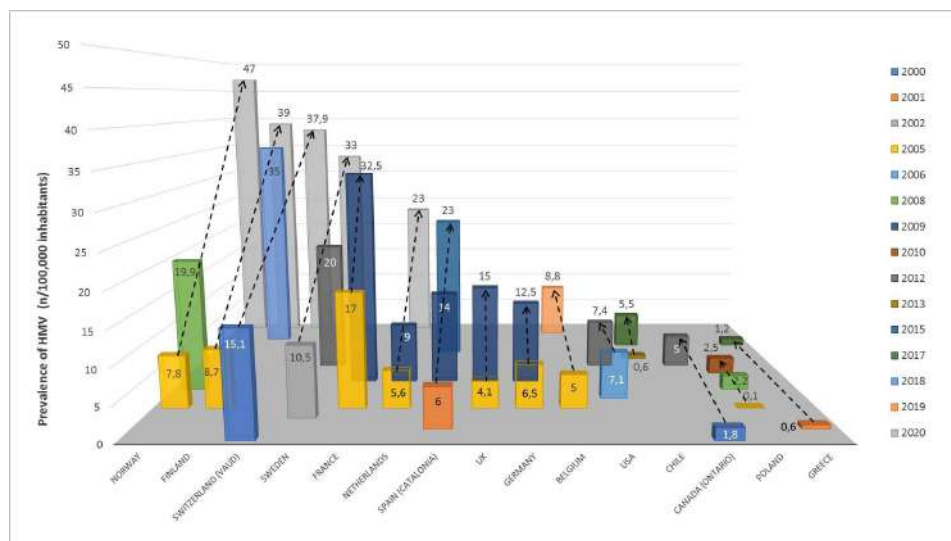


Figure 4 Evolution of the prevalence of HMV in 15 areas. Data by decreasing prevalence of HMV (reference): Norway,^{5,20,42} Finland,^{5,20,43} Vaud (Switzerland),^{44,44} Sweden,^{13,20,22} France,^{5,6} Netherlands,^{5,21} Catalonia (Spain),^{6,6,45} UK,^{5,6} Germany,^{5,6} Belgium,^{5,19} USA,^{45,46} Chile,^{16,47} Ontario (Canada),⁴⁸ Poland^{23,23} and Greece.^{5,17} HMV, home mechanical ventilation.

aims to support secretion management by lung volume recruitment prior to coughing,⁵² or to improve lung function of patients with NMDs, as illustrated in a low-income country.⁵³ Mechanical insufflation exsufflation devices alternate positive and negative pressure. Such devices are able to recruit volume, assist cough and clear secretions out of the bronchial tree with minimal participation of respiratory muscles.^{51,52}

Services for HMV

Service delivery involves both the provision of technical implementation and education at the initiation of treatment, including a follow-up service at home.⁸ The organisation of technical assistance (24/24 hours in case of continuous HMV) via a dedicated respiratory support call centre is critical to minimise the risk for patients.⁵⁴ Service delivery also includes the cost of homecare and maintenance of equipment. Given the large variation in the organisation and financing of local healthcare systems across the world, we do not discuss the cost of care and service delivery in this review. We focus on the cost of supplying HMV equipment, which includes the ventilators and accessories.

Cost for HMV equipment

Ventilators

The purchase of ventilators represents the largest costs related to HMV. In the Czech Republic, an affordable bilevel ventilator and related accessories cost 2 400€. Bilevel devices are cheaper (<4000€) than life-support ventilators (>6500€). Considering the bilevel lifespan over 7 years based on the authors' experience, 1 year of treatment costs 630€, which includes accessory changes 1x/year.⁹ In Asia, inexpensive bilevel devices between 350€ and 600€ were developed to make HMV possible at low cost. A backup power supply unit can be provided for 160€ to support 24-hour ventilation at home in India.⁴⁰

Accessories

In general, tubing is available at low prices (5–20€). Nasal masks (35–180€) are less expensive than oronasal masks (90–300€). Usually, accessories are cheaper in developing than in developed countries. Differences in the rate of replacement and reimbursement of accessories across countries impact on the cost for HMV equipment.⁵⁵

Cost for HMV equipment in NMDs

Figure 5 provides an original algorithm to calculate an annual workable budget for HMV in patients with NMDs, per 100 000 inhabitants. It considers the prevalence of the three categories, nocturnal, discontinuous and continuous NIV. This algorithm

aims to provide a rough estimation of the annual cost for HMV equipment according to low versus high budget allocated to HMV. Obviously, many combinations of equipment and cost exist between the low and high budgets in figure 5.

The calculation considers a minimum of 6-year amortisation of HMV equipment and includes the provision of two masks and tubing/year. As suggested in figure 5, patients with NMD can be offered HMV from around 504€/year/100 000 population when using inexpensive bilevel devices. This corresponds to ±168€/patient with NMD/year. Such low costs, corresponding to 10% of that in high-income countries, highlights why LMICs may find it possible to provide low-cost HMV.

The high budget suggests offering HMV from ±5040€/year/100 000 population, corresponding to ±1680€/patient with NMD/year. However, services, maintenance, reparations, delivery of humidification systems, suction units and chin straps (if needed), filters, resuscitation bag, additional external batteries and other accessories are not included in this budget. When considering all services and equipment, the reimbursement of HMV leads to greater costs. For example, reimbursement of nocturnal ventilation may reach 3232€, 5037€ and 5760€/patient/year in France, Belgium and South Korea, respectively.^{15,56,57}

FACTORS INFLUENCING THE SUCCESS OF HMV DEVELOPMENT

There is a considerable number of interacting factors affecting the success of HMV development.

Reimbursement policies and network

Adequate reimbursement policies as well as an organised and functional network are essential for HMV implementation.²⁵ The lack of full reimbursement hampers the development of HMV in most LMICs, however, during the past few years, the situation has improved in Europe.⁵⁸ There may be either no reimbursement at all (Ukraine, Bosnia and Herzegovina) or partial reimbursement such as in children (Bulgaria), in NMD (Serbia, Romania) or in the case where invasive ventilation is used as interface (Czech Republic). In Russia, candidates for HMV initially relied either on charitable foundations or on the patients and families themselves. In 2019, the Russian Ministry of Health introduced a system where the purchase and delivery of HMV equipment are made by state hospitals. In Poland (2004), the National Health Fund reimbursed HMV through public health funding. Since then, a rapid increase in HMV prevalence was observed, indicating the importance of public funding.²³

To achieve a satisfying life, patients with HMV require help from a variety of health and social care services, community services as well as care from the family.⁵⁹ Centres for HMV ensure the

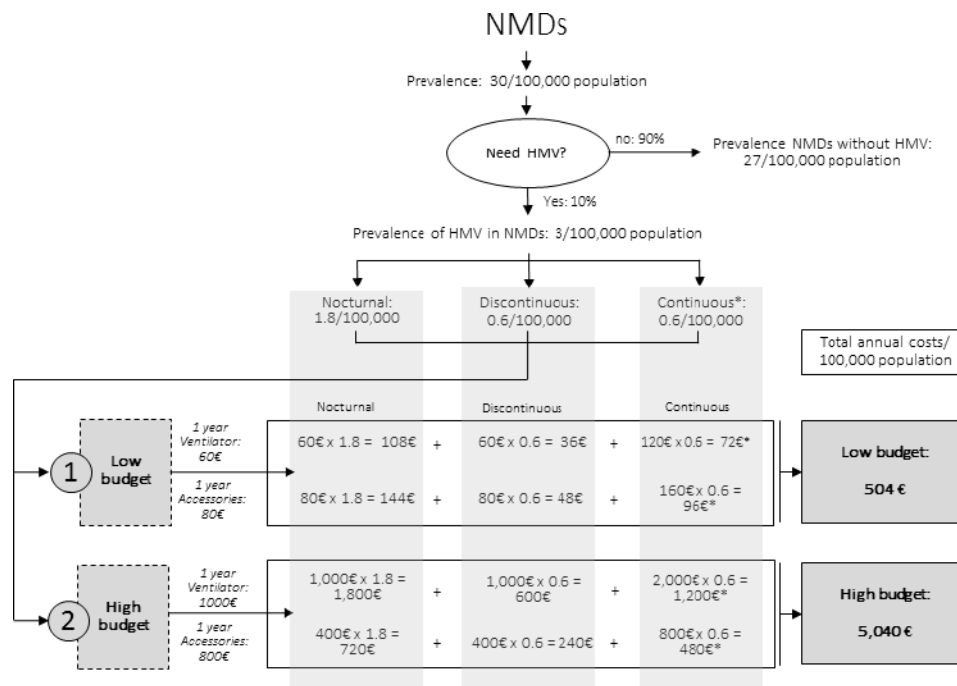


Figure 5 Estimation of the annual cost for HMV equipment in NMDs (/100,000/population). * Two devices are needed for continuous HMV. HMV, home mechanical ventilation; NMDs, neuromuscular disorders.

selection of the right patients, the timely initiation of adequate ventilation and monitoring during regular long-term follow-up.⁶⁰ The network should facilitate the distribution of the responsibilities at different levels: the social work department for home discharge, the providers of HMV equipment delivery, the HMV specialists for long-term follow-up, the personal support worker at home and the availability of contacts in case of technical or medical emergencies.⁶¹

Dedicated centres for HMV

Centralisation of care in few dedicated centres for HMV, concentrating the experience of HMV, is desirable.²⁵ In the historical survey by Lloyd-Owen *et al*, as few as 65 HMV users on average were followed up per centre.⁵ In order to maximise the effectiveness and minimise costs for centres for HMV, Denmark and the Netherlands have limited the number of centres providing HMV.⁵ In the Netherlands, patients were split into four national centres: each centre covering a general population of 4.3 million inhabitants. Comparatively, in 2005, there were 4.4 x, 6 x, 12.6 x, and 31 x more centres in Poland, Belgium, Portugal, and Sweden, respectively.⁵ The largest and least inhabited countries accounted for many centres, each concentrating on fewer HMV users.¹³

Role of international cooperation

Examples of emerging programmes of HMV in developing countries demonstrate the positive impact of international cooperation, such as between Serbia and France in 2005,²⁵ and between Chile and Germany in 2006.¹⁶ After donations of secondhand ventilators, a successful programme for HMV was established and subsequently subsidised by local health authorities, highlighting the importance of developing care and financing together. Such successful cooperation substantiates that secondhand devices, used in developed countries for 5 or 6 years but due for replacement, should be fit for use for an additional few years in LMICs.

Socioeconomic conditions

It is obvious that socioeconomic conditions impact the development of HMV. However, there are numerous studies from LMICs concluding that HMV can be initiated in developing countries. In South Africa³⁴, an LMIC, HMV was deemed as feasible despite difficult socioeconomic circumstances. Survival outcomes were comparable to high-income countries with HMV. An underlying medical condition was the only independent significant risk factor for mortality.⁴⁹ In Poland (2010), the most important

factors, which originally inhibited the development of HMV, were the omission of respiratory physicians in the process of qualification, the absence of any national guidelines and the sophisticated demands for HMV equipment.¹¹ In Canada¹⁴, important perceived barriers to HMV were the insufficient funding for paid caregivers and equipment for HMV.¹⁴ However, it is hard to differentiate the costs for the care of people with a disability in general from the supplemental care related to HMV. Again, the socioeconomic conditions do not appear to be the only parameter limiting the prevalence of HMV. Enthusiasm and willingness to develop HMV explain, in part, why high-income countries insufficiently develop HMV and why some LMICs make inspiring efforts to develop it.²⁴

Requirements of local authorities

The initiation of HMV should meet the requirements of the local authorities regarding the equipment specifications for HMV. The initiation of a pilot programme of HMV in Ukraine in 2021, using 10 secondhand ventilators donated from abroad, met unexpected barriers.⁶² Quite logically, the Ministry of Health in Ukraine required an assurance (especially during the COVID-19 pandemic) that the manuals and guides for all ventilation equipment for HMV were available in Russian language (devices and accessories). On one hand, ventilators were not reimbursed, but, on the other hand, donation was challenging, suggesting that stringent regulations can prove, to some extent, a hindrance to the development of care.

One should be inspired by trials to make low-cost 'custom-made', and easy-to-build non-invasive pressure support ventilators for hospital use, potentially leading to the development of equipment for HMV in LMICs, provided that such devices can obtain official recognition to be used at home.⁶³

Developing expertise for NIV in acute care

Implementation of HMV is challenging when NIV is not used on regular basis in acute care units in LMICs, leading to the lack of equipment and skills of the medical staff.⁶⁴ Usually in LMICs, only a few clinical centres with enthusiastic leaders use NIV to treat acute respiratory failure, whereas, for the majority of patients, acute NIV is not available. Without acute NIV, it is not easy to implement long-term NIV for home use, since most of eligible patients would be recruited after an acute episode. To bridge this gap, between 2016 and 2019, the Ministry of Health in Poland financed the development of beds in specialist wards providing acute NIV care across Poland. This highly cost-effective programme, reducing

in-hospital mortality, could be adapted and introduced in other LMICs.⁶⁵

Training of local medical staff

Knowledge about the pathophysiology of respiratory failure, principals of operation of HMV devices, circuits and interfaces should be shared in the training of involved medical staff.⁶² Since 2012, the Polish Society of Respiratory Diseases has run 2–3 days hand-on workshops for about 30–40 doctors and the same number of nurses.⁶⁶ Three editions are running every year: basic, advanced and home NIV. To date, about 1000 professionals have been trained. Hence, efforts should be concentrated on assisting local leaders in NIV in adapting such educational programme in all LMICs. Assistance should cover preparation of presentations, and teaching materials and support by experts, in person during workshops.⁶² The creation of a guideline for HMV would be the pinnacle of success. The assistance and cooperation, with experts from developed countries, would be invaluable for leaders from LMICs.

The burdens of care and financial constraints for family members

The everyday care of disabled patients dependent on HMV is an even more demanding issue than providing and operating a ventilator. In LMICs, the social care is underdeveloped and this issue usually falls on family members who have to take responsibility themselves or hire a caregiver out of personal funds. In this scenario, families in LMICs have to assess whichever option is better for them. Public caregivers are available in most LMICs, but they can serve only a few hours a day, which does not enable full-time employment for the family member. If a family is not able to perform full-time care or afford hiring a qualified caregiver, patients have to be placed in stationary facilities, which exist in most European LMICs, but their availability may be an issue.

CONCLUSIONS

This review reports updated prevalence data of HMV. The prevalence of HMV is estimated at 7.3/100 000 inhabitants, all diseases combined. The prevalence of NMDs is estimated about 30/100 000 inhabitants, of which 10% would use HMV. The group-specific prevalence of patients with NMD prescribed HMV is estimated about 3/100 000 population.

Our review clearly shows that a nation's economy has a crucial impact on medical care. Since HMV is a method of treatment requiring sophisticated technology, the impact on this field seems to be even bigger, which contributes to large discrepancies in availability of HMV among countries, depending on their income. Thereupon, cooperation with developed countries may play an important role in accelerating the development of HMV in LMICs.

Our review concentrates on the technical needs of HMV. However, the provision of equipment does not meet all the needs of patients receiving HMV. Equally important is a system of care for these patients, with various needs and problems, which includes assessment of the timing of HMV, mode of initiation and long-term follow-up. The model of HMV differs from country to country, suggesting that none is perfect. That is why countries with HMV programme aspirations have a unique opportunity to benefit from experiences acquired by developed countries and thereby create their own, more comprehensive, patient-oriented and cost-effective system, in which we believe data presented in this article will be helpful.

This review proposes a method of calculation of the cost for equipment in NMDs per 100 000 inhabitants. Evidence from emerging countries suggest that a minimal budget of about 168€/patient with NMD per year, including the cost of equipment without any service, can address the cost of HMV equipment in LMICs. In high-income countries, a minimal budget of about 1680€/patient/year can address the cost of HMV. However, when the maintenance of equipment and services is included in the budget, it can increase between 3232 and 5760€/patient/year. There is a positive relationship between the prevalence of HMV and markers of wealth and development. Adequate reimbursement

policies as well as an organised and functional network are essential for the implementation and development of HMV. However, the willingness of both healthcare professionals and patient associations can inspire health leaders who are equally concerned about the crucial importance of effective respiratory care of all health consumers in their jurisdiction.

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Investigação respiratória no Reino Unido: investir nos próximos 10 anos

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Em Julho de 2021, o *Office of Life Sciences* (OLS)¹ do Reino Unido publicou uma Visão das Ciências da Vida para o Reino Unido, destacando áreas chave de ação. O relatório assinalou especificamente a redução da morbilidade e mortalidade por doença respiratória como uma das sete prioridades da missão de saúde. Adicionalmente, o relatório enfatizou de forma mais geral a necessidade de apoiar as infraestruturas de apoio para permitir uma melhor utilização dos dados de saúde e dos dados genómicos e aumentar a eficiência da prestação de investigação clínica no sentido da melhoria dos cuidados de saúde.

A importância de uma próspera comunidade de pesquisa de doenças respiratórias no Reino Unido também ganhou um grande destaque com a pandemia da COVID-19. O Reino Unido conquistou o reconhecimento internacional pela sua capacidade de realizar ensaios terapêuticos definitivos sobre a COVID-19 e também realizou grandes investimentos em investigação sobre a síndrome da pós-COVID-19 através do UKRI e do NIHR, que irão continuar a informar a prática clínica. Contudo, subsiste uma questão essencial: até que ponto a comunidade de investigação respiratória está bem preparada para realizar a visão da OLS?

Dois exercícios de consulta recentes podem proporcionar mais algum conhecimento sobre o estado da investigação respiratória no Reino Unido. O primeiro foi concebido para identificar áreas prioritárias de atenção e ocorreu entre 2017 e finais de 2019 por meio de um grupo reunido de forma informal pela *UK Respiratory Research Collaborative* (UKRRC). Incluiu duas sessões abertas multidisciplinares realizadas na reunião de Inverno da *British Thoracic Society* e reuniões com os principais interessados, incluindo as principais instituições de caridade respiratória e um leque de líderes de opinião. Infelizmente, a pandemia surgiu antes da conclusão deste trabalho, mas mesmo assim forneceu valioso conhecimento aos interessados. Uma outra mesa redonda de alto nível com o governo convocada pela *Asthma+Lung UK* reforçou a necessidade de uma nova abordagem.

Neste artigo, resumimos as principais mensagens que resultaram das consultas realizadas pela UKRRC e pela *Asthma+Lung*

UK e revemos as mudanças provocadas pela pandemia. Identificamos áreas-chave nas quais, enquanto especialidade, nos devemos concentrar para assegurar que o Reino Unido está posicionado para enfrentar o desafio lançado pela visão da OLS e fazer sugestões sobre como enfrentar este desafio.

CARGA DE DOENÇA

Qualquer priorização da agenda de investigação respiratória requer dados precisos sobre a carga de doença subjacente. A *British Lung Foundation* (agora *Asthma+Lung UK*) tem apoiado, no passado, o fornecimento de estimativas da carga de doença, mas os dados precisos com base em inquéritos à população em geral estão atualmente bastante datados. A *Health Survey for England* 2010 e a *Scottish Health Survey* 2008-2010 descobriram que aproximadamente uma em cada cinco pessoas no Reino Unido (~12.7 milhões) relatou antecedentes de asma, doença pulmonar obstrutiva crónica (DPOC) ou outra doença respiratória. Metade destas relatou ter tomado medicamentos receitados para doença pulmonar no último ano. De acordo com estas estimativas, os registos clínicos gerais sugerem que, em 2012, cerca de 8 milhões de pessoas no Reino Unido foram diagnosticadas com asma, 1,2 milhões com DPOC e mais de 0,4 milhões com outras formas de doença pulmonar. A DPOC continua a ser a segunda maior causa de admissão em urgência hospitalar e custa ao NHS 1,9 mil milhões de libras por ano. O Reino Unido também tem, em geral, piores resultados de doença pulmonar do que o resto da Europa (especialmente mortalidade por asma, prevalência de asma, prevalência de DPOC e taxas de cancro do pulmão). De forma a contextualizar esta situação, estão também disponíveis estimativas do *Global Burden of Disease Study*, que, para 2017, sugeriu que, em todo o mundo, cerca de 550 milhões de pessoas sofrem de doença respiratória crónica, um aumento de 40% desde 1990.²

Em 2011-2012, as doenças pulmonares foram responsáveis por 20% de todas as mortes no Reino Unido, 8% de todas as hospitalizações e 10% de todos os dias de internamento.

Desde Janeiro de 2020, a pandemia da COVID-19 aumentou a importância relativa da doença respiratória como causa de morbilidade e mortalidade no Reino Unido. Desde Abril de 2022, verificaram-se 21,8 milhões de casos de COVID-19, resultando em 823000 hospitalizações e 171000 indivíduos morreram nos 28 dias seguintes à infeção por COVID-19.³ Os dados atuais da ONS para o Reino Unido sugerem que cerca de 1,3 milhões de pes-

soas sofrem atualmente de sintomas de síndrome da pós-COVID-19. As estimativas também sugerem que a fibrose pulmonar relacionada com a COVID-19 pode resultar numa duplicação do número de pacientes que sofrem de doença pulmonar intersticial, embora tal necessite de confirmação. Adicionalmente, a pandemia alterou significativamente o acesso a vias clínicas para aqueles com doenças diferentes da COVID-19, resultando num grande aumento do número de pacientes em listas de espera e em apresentações atrasadas de pacientes com outras doenças respiratórias.

As mudanças nas exposições ambientais também irão alterar a longo prazo a carga de doença. Embora a redução das taxas de tabagismo e a melhoria geral da qualidade do ar sejam obviamente bem-vindas, ainda há muito por fazer, particularmente na compreensão das consequências da alteração de padrões de exposição impulsionada pela qualidade do ar na interface interior e exterior e dos potenciais efeitos de uma alteração para uma rede de carbono zero. O uso crescente de produtos de *vaping* pode ter efeitos a longo prazo na saúde respiratória. O número de pessoas com obesidade também está a aumentar. Verificam-se alterações devido à influência das desigualdades socioeconómicas e outras na condução do risco de desenvolvimento de doenças pulmonares e na alteração da facilidade de acesso às vias de saúde. Estes também são temas destacados no relatório da OLS.

ALTERAÇÕES NOS MODELOS DE PRESTAÇÃO DE CUIDADOS DE SAÚDE E INVESTIGAÇÃO

Os modelos de prestação de cuidados de saúde estavam a mudar no Reino Unido antes da pandemia, mas estas mudanças foram aceleradas pela COVID-19. Cada vez mais, os cuidados de saúde são prestados na comunidade ou de forma remota, em vez de serem prestados em hospitais-escola. Atualmente, um número mais elevado de pacientes apresenta comorbidades significativas que requerem uma abordagem mais personalizada dos cuidados de saúde. A forma como os ensaios clínicos são realizados também está a mudar, com o uso crescente de ensaios de “vida real” que avaliam intervenções no contexto dos cuidados de saúde habituais, em vez do tradicional cenário de ensaios clínicos aleatorizados controlados por placebo, e mais ensaios que adotam um desenho Bayesiano, sendo o ensaio *RECOVERY* (avaliação aleatorizada da terapêutica COVID-19)⁴ um exemplo clássico. O acesso a dados de saúde para investigação continua a ser um desafio, mas o acesso melhorado a dados clínicos para a investigação relacionada com a COVID-19 sublinha a forma como os estudos de investigação podem ser “acelerados” para fornecer resultados o mais rapidamente possível. As abordagens de equipa multidisciplinar à doença são cada vez mais importantes. Todas estas mudanças precisam de ser tidas em consideração quando se revisitam os modelos de desenvolvimento da investigação.

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Caixa 1 Oito ações chave

1. Racionalizar e ampliar os conjuntos de dados essenciais sobre a incidência, prevalência e resultados de doenças respiratórias para fornecer acesso aberto centralizado a dados que são regularmente atualizados de modo a facilitar a investigação e a prestação de cuidados de saúde.
2. Estabelecer um observatório de monitorização para examinar os fatores de risco de doença respiratória e modelizar as mudanças previstas nos padrões de doença.
3. Priorizar iniciativas de deteção de casos de doença respiratória não diagnosticada, incluindo uma análise universal dos cuidados de saúde pulmonares.
4. Estabelecer um grupo de trabalho para aumentar o acesso a terapêuticas eficazes em doenças respiratórias, com particular atenção aos grupos "de difícil alcance".
5. Criar centros virtuais de excelência no Reino Unido para diferentes doenças respiratórias de modo a facilitar a realização de estudos de investigação clínica, com o objetivo de trabalhar em todo o sector dos cuidados de saúde para melhorar a eficiência através de uma colaboração eficaz.
6. Criar grupos de trabalho para subfenotipagem e redefinição de doenças respiratórias e para elaborar recomendações de investigação para futuras abordagens terapêuticas.
7. Estabelecer um grupo de trabalho e conclusão para explorar as barreiras que impedem os estagiários de prosseguir carreiras na investigação respiratória e para identificar incentivos ao aumento da capacidade futura.
8. Estabelecer um grupo estratégico intersectorial no Reino Unido para proporcionar liderança e supervisão do portefólio de investigação respiratória, para monitorizar o progresso em ações essenciais e a concretização da Visão OLS.

A CAPACIDADE DO REINO UNIDO PARA DESENVOLVER INVESTIGAÇÃO RESPIRATÓRIA

O Reino Unido tem a sorte de, no passado, ao longo de um período alargado, os investigadores baseados em instituições britânicas terem liderado a investigação internacional sobre doenças respiratórias. Em Inglaterra, o investimento através do NIHR em Centros de Investigação Biomédica e redes de ensaios clínicos, como o fornecido pela *Respiratory Translational Research Collaboration* e as

redes de cuidados primários, proporciona algum apoio em termos de infraestrutura. No entanto, o nível de investimento fica aquém de outras áreas de especialidade, com menos de 2% da despesa em investigação de saúde a apoiar diretamente a investigação de doenças respiratórias (excluindo o cancro), em contraste com os dados do relatório CRC de 2018, que mostra que as doenças respiratórias são responsáveis por 6% dos anos de vida ajustados pela incapacidade no Reino Unido.⁵ Os dados da *Public Health England* também mostram grandes diferenças na carga de doença a nível regional e nacional, resultando em desigualdades substanciais nos cuidados de saúde que continuam por resolver.

Existe uma preocupação sobre o declínio do número de académicos que expressam o desejo de seguir uma carreira na investigação respiratória e sobre a redução dos cargos académicos clínicos na especialidade. O inquérito de 2017 a nível do Reino Unido sobre bolsas de investigação clínica e de saúde revela que apenas 3% das bolsas foram concedidas à medicina respiratória em comparação, por exemplo, com 23% ao cancro. A medicina respiratória também sofre de uma relativa falta de financiamento beneficente e, embora a recente fusão da BLF e da Asthma UK numa única instituição de beneficência deva ajudar a aumentar o apoio estratégico da *Association of Medical Research Charities* (AMRC) e do resto do terceiro sector, o nível geral de financiamento disponível é muito inferior ao de outras áreas, como o cancro e as doenças cardiovasculares. Embora continue a existir um setor SME próspero no Reino Unido, várias grandes empresas farmacêuticas fecharam ou realocizaram os seus laboratórios de investigação respiratória do Reino Unido para o estrangeiro, reduzindo ainda mais as infraestruturas.

UM PLANO DO REINO UNIDO PARA A INVESTIGAÇÃO RESPIRATÓRIA

Do nosso ponto de vista, este é o momento para uma revisão radical da forma como realizamos investigação respiratória no Reino Unido para lidar com as alterações nos padrões da doença e da prestação de cuidados de saúde. Acreditamos firmemente que a investigação precisa de estar firmemente inserida na prática clínica de rotina em todo o NHS de modo a responder a este desafio.

RESPONDER À MORBILIDADE E MORTALIDADE RESPIRATÓRIAS

Para responder completamente à morbidade e mortalidade respiratórias, precisamos de um melhor acesso a dados transversais contemporâneos sobre saúde respiratória no Reino Unido, que são atualizados periodicamente. Uma parte da solução poderá ser repetir a componente respiratória do *Health Survey for England* 2010 num futuro próximo, mas é necessária uma monitorização contínua da incidência e prevalência da doença, por exemplo, para definir o impacto a longo prazo da COVID-19 na carga de doença.

Por isso, devemos maximizar as oportunidades proporcionadas pela integração de dados de saúde em todo o NHS, indústria e academia através do trabalho colaborativo com a *Health Data Research UK* e a *NHS Digital* para garantir que maximizamos os benefícios dos conjuntos de dados de saúde relevantes. Isto deve incorporar as coortes respiratórias existentes e novas. O novo programa "*Our future Health*" representa mais uma oportunidade. Acreditamos que a inclusão da espirometria para 1 milhão de pessoas inscritas no programa "*Our Future Health*" e a identificação de uma subcoorte (~5000-10 000) dentro deste programa, na qual poderíamos medir os biomarcadores respiratórios sequencialmente ao longo de 10 anos para compreender os primeiros marcadores de doença e identificar novos alvos terapêuticos, seriam valiosas.

No entanto, estas medidas por si só não identificarão todos aqueles em risco de desenvolver doenças pulmonares. Recomendamos a todos no Reino Unido que façam um exame de saúde pulmonar aos 25 anos de idade e, depois, periodicamente (talvez a cada 5 anos) para identificar as pessoas com doença pulmonar e tratá-las precocemente (através da cessação do tabagismo, intervenção ocupacional e tratamento precoce de novas doenças respiratórias).

De modo a prever as tendências futuras das doenças, teremos de quantificar com precisão a contribuição da poluição do ar exterior e interior e outros fatores ambientais, bem como dos fatores socioeconómicos, da obesidade e da multimorbilidade para a carga de doenças respiratórias no Reino Unido. Isto irá permitir desenvolver melhores modelos preditivos para estimar o efeito da alteração da exposição ambiental e de outros fatores na saúde respiratória. De forma a melhorar o acesso aos cuidados de saúde, precisamos de encontrar melhor os casos de doenças pulmonares comuns e mais raras, particularmente nos cuidados primários, para assegurar um diagnóstico e tratamento precoces, o que sublinha a necessidade de melhores diagnósticos.

Precisamos de novas e melhores terapêuticas para as muitas doenças respiratórias em que os resultados continuam a ser fracos. De modo a responder a isto, devemos abraçar totalmente sistemas e abordagens multiómicas para as doenças respiratórias e melhorar o apoio à investigação laboratorial que isso requer. Também precisamos de desenvolver novas tecnologias para monitorizar e apoiar os pacientes de forma mais eficaz. Tudo isto deve ser realizado com o reforço da participação do público e dos pacientes na cocriação de novos 'produtos', sejam eles farmacêuticos, dispositivos, intervenções ou novas vias de cuidado.

CAPACIDADE E INFRAESTRUTURA DE ENDEREÇAMENTO

De modo a assegurar a capacidade de continuar a desenvolver programas de investigação existentes nas ciências básicas e clínicas relevantes para a doença respiratória e para

apoiar novos programas de investigação, o Reino Unido precisa urgentemente de resolver o declínio das infraestruturas académicas e industriais. Devemos desenvolver rapidamente novos centros de investigação nacionais colaborativos físicos ou virtuais de excelência e redes que se concentrem em abordagens multidisciplinares para responder às principais prioridades de investigação respiratória.

É necessário continuar a desenvolver fortes ligações de colaboração entre o meio académico e a indústria. Como discutido na Visão OLS, devemos aumentar a atratividade global do Reino Unido para a investigação e inovação respiratória colaborativa industrial e mitigar quaisquer efeitos do Brexit. Devemos assegurar que o Reino Unido continua a contribuir e a liderar os programas de investigação e inovação colaborativos internacionais através da Horizon Europe e de outras colaborações internacionais. Temos também a obrigação moral de continuar a apoiar a investigação global em saúde sobre as causas e impacto das doenças respiratórias, que tem sido afetada pela recente redução no apoio ao orçamento de apoio internacional do Reino Unido.

Uma consequência da pandemia tem sido o 'acelerar' das aprovações regulatórias para a investigação relacionada com a COVID-19, incluindo processos mais simples de acesso a dados de saúde. No entanto, à medida que vamos emergindo da pandemia, existe um grande risco de regressarmos às abordagens pré-pandémicas das aprovações de investigação, o que seria uma verdadeira oportunidade perdida de alteração. Devemos procurar adotar os benefícios para a investigação de processos de governança de investigação mais acelerados e simples, para além da mera investigação da COVID-19.

Por fim, para assegurar que podemos cumprir estes objetivos, devemos remover as barreiras aos estagiários que desejem integrar a investigação clínica. É necessário determinar quais são as principais barreiras que impedem os estagiários médicos e profissionais associados de prosseguirem carreiras de investigação e implementar ações para as mitigar. É necessário estabelecer metas mínimas para o número de estagiários de investigação nos diferentes grupos profissionais de modo a assegurar que a massa crítica seja mantida e monitorizar o número de estagiários em conformidade. No sentido de ajudar a atingir este objetivo, é necessário melhorar a flexibilidade da formação tanto para os médicos como para os profissionais de saúde associados e melhorar a tutoria para todos os estagiários interessados na investigação nas fases iniciais da sua formação.

REDEFINIR AS DOENÇAS RESPIRATÓRIAS

Dada a elevada carga das doenças respiratórias crónicas, é necessário melhorar a nossa capacidade de identificar sub-fenótipos de doenças e adaptar as intervenções específicas dos pacientes àqueles que mais prova-

velmente beneficiarão delas. Isto tem sido conseguido até certo ponto, por exemplo, com terapias que visam a asma grave provocada por Th2, o uso de modificadores CFTR na fibrose cística e abordagens de medicina de precisão à quimioterapia do cancro do pulmão, mas ainda há muito a fazer em muitas outras doenças respiratórias. Também devemos dar prioridade a intervenções destinadas a reduzir a exposição a causas ambientais daqueles com maior risco de doença respiratória ao longo da vida de forma a reduzir a carga de doença no futuro: isto requer melhores modelos preditivos de risco individual.

MELHOR PRESTAÇÃO DE SERVIÇOS

É necessário promover mais investigação para definir os modelos de prestação de serviços mais eficientes para lidar com a crescente carga de trabalho, tanto nos cuidados primários como secundários, devido a doenças respiratórias numa população em envelhecimento e identificar modelos de prestação para assegurar que os grupos "de difícil alcance" nas nossas comunidades tenham acesso a cuidados de saúde e oportunidades de investigação. Um elemento essencial será promover a ativação e o envolvimento dos pacientes através de um melhor apoio à autogestão e assegurar que os programas e produtos digitais de autogestão são concebidos segundo as necessidades e comportamentos de todos os pacientes.

A criação dos Sistemas Integrados de Cuidados (ICS) em Inglaterra e um maior foco nos cuidados em todo o sector de cuidados primários e secundários nas nações em desenvolvimento proporciona uma oportunidade de melhorar a coordenação das vias de cuidado da doença em todo o serviço de saúde. É animador que a investigação seja um elemento essencial no enquadramento do desempenho dos ICS. Contudo, muitos ICS possuem pouca experiência de investigação, pelo que o trabalho em conjunto com parceiros académicos será fundamental.

Também necessitaremos de abordar mais detalhadamente a interação entre os sintomas respiratórios e a multimorbilidade/fragilidade através de uma abordagem centrada na pessoa e não nos órgãos, incluindo a investigação sobre os papéis da saúde mental, da obesidade e do descondicionamento como causas da falta de ar. Estas abordagens também devem ajudar a lidar com o impacto da COVID-19 longa sobre a população.

CONCRETIZAR A VISÃO OLS

A concretização do objetivo da missão de cuidados de saúde na Visão OLS para as Ciências da Vida necessita de um plano estratégico de 10 anos com marcos relevantes e monitorização incorporados. Embora seja essencial maximizar a utilização dos recursos existentes, é improvável que tudo possa ser alcançado sem um investimento adicional significativo. Devemos defender a

priorização de esquemas de financiamento tais como os apoiados pela UKRI e pela Innovate UK para apoiar as prioridades da OLS listadas acima. A concretização desta visão exigirá também um investimento significativo da indústria para que possamos desenvolver os novos medicamentos, diagnósticos, dispositivos terapêuticos e tecnologias para transformar os resultados de saúde em parceria. Finalmente, a coordenação global será essencial. Atualmente, não existe uma estrutura única para assegurar que isto ocorra eficazmente e é necessário criar uma. Para facilitar esta situação, acreditamos que é altura de reunir os principais financiadores atuais da investigação respiratória, incluindo o NIHR, os conselhos de investigação, a indústria e os membros da AMRC para desenvolver a estrutura de modo a maximizar a capacidade da comunidade de investigação respiratória para realizar a visão da OLS. Isto exigirá ações integradas em todas as comunidades de saúde, para evitar que a investigação aconteça em silos desconectados: as tarefas principais estão destacadas na caixa 1.

A Visão OLS proporciona um desafio à comunidade respiratória com que devemos nos comprometer. Tanto a saúde da nossa população como a futura posição internacional da nossa investigação respiratória dependerá em grande parte da forma como abordarmos esta visão ao longo dos próximos anos.

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Características da sazonalidade transposta da epidemia de VSR no Reino Unido e na Irlanda em 2021: análise dos primeiros 10 000 pacientes

As intervenções não farmacêuticas (INF) introduzidas globalmente para limitar a propagação do SARS-CoV-2 levaram à perturbação da sazonalidade típica do vírus respiratório sincicial (VSR).¹ Os estudos que examinaram o ressurgimento do VSR têm sido limitados pelo tamanho da amostra e pela falta de informação sobre episódios e características clínicas dos cuidados secundários. O estudo *BronchStart* é um estudo de coorte multicêntrico prospectivo. Os serviços de urgência pediátrica (SUP) dentro do PERUKI (*Paediatric Emergency Research in the UK and Ireland*) submetem dados sobre todas as crianças com menos de 2 anos de idade que visitam um SUP com sintomas de infecção aguda do trato respiratório inferior (diagnosticada como bronquiolite, infecção do trato respiratório inferior ou primeiro episódio de pieira aguda). A informação de seguimento é submetida 7 dias depois e os dados dos estudos são disponibilizados num dashboard online ao vivo alojado pela *Microreact*.²

Apresentamos dados iniciais de 10 347 bebés e crianças de 44 locais de estudo para o período de 1 de Junho a 5 de Dezembro de 2021. A epidemia de VRS no Reino Unido em 2021 terminou com o pico das infeções em Agosto (figura 1A). Comparando a distribuição etária dos bebés hospitalizados

com menos de 12 meses com a dos anos anteriores em dois grandes centros pediátricos participantes no *BronchStart* (*Leicester Children's Hospital* e *Bristol Royal Hospital for Children*), observámos uma distribuição etária semelhante (figura 1B). Isto sugere que a redução da exposição comunitária ao VRS durante os 15 meses que antecederam o início da estação não resultou numa falta clinicamente significativa de transferência de anticorpos maternos protetores para aqueles com menos de 3 meses de idade ou que as INF introduzidas não impediram a transmissão de baixo nível. Ao contrário da Nova Zelândia, o fardo hospitalar global dos internamentos por bronquiolite no Reino Unido e na Irlanda em 2021 foi inferior ao das estações anteriores.³ A doença suficientemente grave para requerer cuidados intensivos foi de 2,5% na nossa coorte (bebés de 6 semanas a 1 ano), que é comparável aos 4,2% relatados no ensaio BIDS (*Bronchiolitis of Infancy Discharge Study*)⁴ (OR com recurso a teste exato de Fisher 0,59, 95% IC 0,31 a 1,18, $p=0,09$). Observámos uma probabilidade reduzida de um teste PCR de transcriptase reversa para SARS-CoV-2 positivo (83 das 4328 crianças testadas (1,9%), das quais 39 eram coinfeções com outro vírus) em crianças que apresentam infecção aguda do trato respiratório inferior.

Em *BronchStart*, observámos um número frequente de idas e internamentos em SUP de crianças de 12-23 meses de idade devidos a VRS positivo: 362 de 1468 (24,7%) internamentos. Este grupo etário, enquanto bebés, teria tido falta de exposição ao VRS como resultado do atraso da epidemia sazonal. A vacinação materna para VRS pode ter um efeito semelhante no futuro e esta observação, se confirmada, apoiaria o futuro seguimento a longo prazo destas crianças nascidas de mães que recebem uma futura vacina contra o VRS.

Os nossos achados iniciais indicam que o pico da infecção do verão de 2021 no Reino Unido e na Irlanda afetou predominantemente os grupos etários mais jovens como nos anos anteriores. A tendência de um menor fardo da doença em 2021 (como demonstrado pelos internamentos em unidades de cuidados intensivos) sugere uma infecção incompleta por VRS da sua população suscetível habitual, sendo potencialmente o resultado de algumas INF em curso (como o uso de máscara e a lavagem das mãos) durante o período do estudo. A penetração incompleta aumenta a possibilidade de uma nova onda de infecção nos próximos meses, sendo que tal ainda não ocorreu.

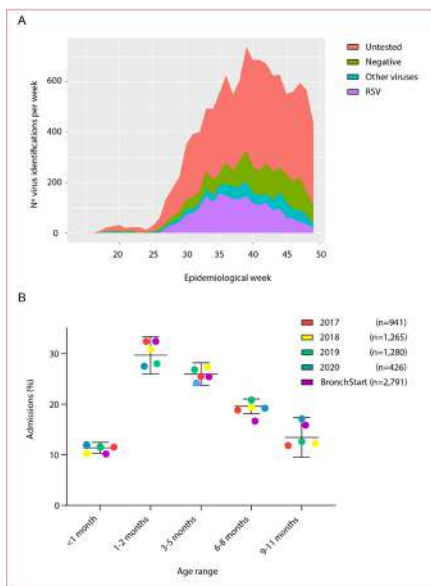


Figure 1 Virus identification over time. (1A) Number of virus infections per week over time. (1B) Comparison of admission rate in *BronchStart* cohort versus data from two paediatric centres (2017-2020). RSV, respiratory syncytial virus.

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			B-LEARNING	PRESENCIAL		
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4	DOENÇAS RESPIRATÓRIAS E OUTRAS PERTURBAÇÕES DO SONO	ROSÁRIO FERREIRA, LIA OLIVEIRA	10, 11, 13	8, 12	18, 31, MAR 2023 1, 14, 15 ABR 2023 5, 6 MAI 2023	16

Módulos:

- 1- Anatomia e Fisiologia do Aparelho Respiratório
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