ORIGINAL RESEARCH LETTER

The impact of the first COVID-19 surge on severe asthma patients in the UK. Which is worse: the virus or the lockdown?

To the Editor:

Respiratory viral infections are a significant cause of morbidity in asthma [1]. Patients with severe asthma were assumed to be at greater risk from novel coronavirus disease 2019 (COVID-19). In the global response to the COVID-19 pandemic, multiple countries enacted social containment policies. In the UK a countrywide lockdown occurred in March 2020, with stringent self-isolation ("shielding") advice for high-risk patients, including people with severe asthma.

Subsequently, the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) reported that 14% of UK patients hospitalised with COVID-19 had an underlying diagnosis of asthma, but they did not associate asthma with higher mortality [2]. The OpenSAFELY study of COVID-19-related deaths identified severe asthma as a factor associated with mortality (hazard ratio 1.13 (1.01–1.26)) [3]. However, "severe asthma" was defined as anyone with asthma and showing a course of oral corticosteroids (OCS) in their records in the past year [3]. Their analysis of inhaled corticosteroid (ICS) use showed increased mortality risk from COVID-19 in asthma patients on high-dose *versus* no ICS, attributed to unrecorded health differences between the two groups [4]. The Italian Severe Asthma Registry reported infrequent incidence of COVID-19, based on participating centres reporting cases of confirmed/highly suspected COVID-19 with severe asthma, and as 21 out of 26 cases were on anti-interleukin IL-5/IL-5R biologics, it was speculated that asthma biologics may modulate the risk of COVID-19 [5]. To our knowledge, there is no information on the burden of social isolation (shielding) in people with severe asthma. There is a need for information on the impact of COVID-19 on a well-characterised severe asthma population in the community, effects of shielding and any association between asthma medication and COVID-19.

The UK Severe Asthma Registry (UKSAR) performed an audit in June 2020 across 14 centres of: patient adherence with shielding advice, potential infection with the COVID-19 virus and outcomes, and asthma control since March 1, 2020. UKSAR centres with >100 registry patients used randomly generated lists to reduce potential bias. Where available, electronic hospital records were checked to confirm hospital admissions and COVID-19 swab/serology results. Permission was obtained by centres as per local audit requirements, and all patients had previously consented to use of their anonymised registry data.

Confirmed COVID-19 was defined as those with a positive PCR/serology test. Suspected COVID-19 was defined as typical symptoms, managed clinically as COVID-19, without a negative test. Ambulatory and hospitalised patients were labelled as "mild" and "severe" COVID-19, respectively. Audit data were combined with clinical data from the UKSAR. We used data from the most recent visit and imputed missing values with data collected at previous visits. Univariate analyses were conducted using independent t-tests, Mann–Whitney U-tests or Chi-squared tests as appropriate. Multivariate analyses were undertaken using logistic regression adjusting for age, sex, ethnicity, body mass index, site, cardiac disease, diabetes and hypertension.

In total, 1365 patients were included (table 1). Shielding advice was sent to 1268 (93.0%) patients, which was followed by 1131 (89.2%). Males and members of a non-shielding household were less likely to follow

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Asthma therapy, including monoclonal antibodies, was not associated with #COVID19 infection or hospitalisation in a UK severe asthma population. Shielding led to a reported worsening of mental health in nearly half of patients contacted (47%). https://bit.ly/3jImUsG

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TABLE 1 Characteristics of severe asthma patients according to coronavirus disease 2019 (COVID-19) status, disease severity and confirmed COVID-19

Characteristic	Subjects	COVID-19 status			COVID-19 disease severity			Confirmed COVID-19	
		No COVID-19	Suspected or confirmed COVID-19	p-value	Nonhospitalised	Hospitalised	p-value	Confirmed COVID-19	p-value[#]
Subjects		1268	97		84	13		19	
Age years	1365	52.8±15.5	51.2±13.8	0.313	50.5±13.8	55.6±13.7	0.215	49.8±13.7	0.404
Male sex	1365	453 (35.7%)	43 (44.3%)	0.089	39 (46.4%)	4 (30.8%)	0.290	5 (26.3%)	0.395
BMI kg·m^{-2}	1166	31.0±7.2	31.3±6.1	0.704	31.3±6.3	31.3±4.9	0.967	30.6±6.3	0.849
Smoking status	1322	–	–	0.584	–	–	0.739	–	0.522
Never-smoker	1322	838 (68.4%)	69 (71.9%)	–	59 (71.1%)	10 (76.9%)	–	15 (78.9%)	–
Ex-smoker	1322	337 (27.5%)	22 (22.9%)	–	20 (24.1%)	2 (15.4%)	–	3 (15.8%)	–
Current smoker	1322	51 (4.2%)	5 (5.2%)	–	4 (4.8%)	1 (7.7%)	–	1 (5.3%)	–
Non-Caucasian ethnicity	1345	150 (12.0%)	18 (18.8%)	0.054	15 (17.9%)	3 (25.0%)	0.553	3 (16.7%)	0.547
Resident in London area	1365	306 (24.1%)	44 (45.4%)	**<0.001**	39 (46.4%)	5 (38.5%)	0.591	11 (57.9%)	**<0.001**
Resident outside London area (rest of UK)	1365	962 (75.9%)	53 (54.5%)	–	45 (53.6%)	8 (61.8%)	–	8 (42.1%)	–
Atopic disease	1236	662 (57.8%)	58 (64.4%)	0.216	48 (62.3%)	10 (76.9%)	0.310	11 (57.9%)	0.991
Depression or anxiety	1365	126 (9.9%)	9 (9.3%)	0.834	9 (10.7%)	0 (0.0%)	0.215	0 (0.0%)	0.148
Clinic FEV_1[¶] % predicted	1113	68.1 (52.9–82.6)	67.9 (59.9–83.4)	0.343	67.9 (59.9–82.8)	73.7 (60.1–84.8)	0.555	80.8 (60.7–86.2)	0.141
Clinic FVC[¶] % predicted	1081	83.6 (71.8–95.4)	82.8 (71.3–92.6)	0.779	83.1 (71.3–91.7)	81.2 (68.9–92.6)	0.814	87.3 (76.7–93.9)	0.558
Asthma medication and control									
ICS dose[¶] BDP equivalent µg	1174	2000 (1600–2000)	2000 (1600–2000)	0.433	2000 (1600–2000)	1000 (800–1600)	**0.002**	1600 (1000–2000)	0.106
Maintenance OCS	1363	481 (38.0%)	34 (35.4%)	0.620	30 (35.7%)	4 (33.3%)	0.872	9 (47.4%)	0.402
Maintenance macrolides	1200	153 (13.8%)	9 (10.2%)	0.351	7 (9.9%)	2 (16.7%)	0.428	3 (16.7%)	0.723
Theophylline	1237	294 (25.7%)	12 (13.2%)	**0.008**	10 (12.8%)	2 (15.4%)	0.800	3 (15.8%)	0.328
Evidence of poor adherence	1190	248 (22.5%)	25 (29.1%)	0.160	18 (24.7%)	7 (53.8%)	**0.033**	6 (31.6%)	0.346
On asthma biologic	1361	853 (67.5%)	65 (67.0%)	0.924	57 (67.9%)	8 (61.5%)	0.652	13 (68.4%)	0.931
Biologic type	917	–	–	0.349	–	–	0.986	–	0.841
Anti-IL-5^{+}	917	680 (79.7%)	55 (85.9%)	–	49 (86.0%)	6 (85.7%)	–	11 (84.6%)	–
Anti-IgE	917	157 (18.4%)	9 (14.1%)	–	8 (14.0%)	1 (14.3%)	–	2 (15.4%)	–
Anti-IL-4/13	917	16(1.9%)	0 (0%)	–	0 (0.0%)	0 (0.0)	–	0 (0.0%)	–
Comorbidities									
Cardiac disease	1299	64 (5.3%)	6 (6.3%)	0.678	5 (6.1%)	1 (7.7%)	0.826	1 (5.3%)	0.992
Diabetes	1365	78 (6.2%)	5 (5.2%)	0.692	5 (6.0%)	0 (0.0%)	0.366	1 (5.3%)	0.873
Hypertension	1365	121 (9.5%)	9 (9.3%)	0.932	7 (8.3%)	2 (15.4%)	0.415	2 (10.5%)	0.885
Malignancy	1365	13 (1.0%)	1 (1.0%)	0.996	1 (1.2%)	0 (0.0%)	0.693	0 (0.0%)	0.657
Associated COPD	1365	38 (3.0%)	5 (5.2%)	0.241	4 (4.8%)	1 (7.7%)	0.657	1 (5.3%)	0.567
Shielding and asthma control during lockdown									
Advised to shield	1363	1182 (93.2%)	86 (90.5%)	0.320	76 (90.5%)	10 (90.9%)	0.963	16 (88.9%)	0.470
Followed shielding advice	1268	1058 (89.5%)	73 (84.9%)	0.182	64 (84.2%)	9 (90.0%)	0.631	13 (81.3%)	0.286
Shielding affected mental health	1237	544 (47.1%)	38 (46.9%)	0.980	33 (46.5%)	5 (50.0%)	0.835	8 (53.3%)	0.629

Continued

TABLE 1 Continued

Characteristic	Subjects	COVID-19 status			COVID-19 disease severity			Confirmed COVID-19	
		No COVID-19	Suspected or confirmed COVID-19	p-value	Nonhospitalised	Hospitalised	p-value	Confirmed COVID-19	p-value[#]
Contracted COVID-19 before shielding advice	76	0 (0.0%)	44 (57.9%)	–	40 (60.6%)	4 (40.0%)	0.219	8 (53.3%)	–
Non-shielding household	1338	715 (57.3%)	50 (54.9%)	0.656	41 (51.2%)	9 (81.8%)	0.056	14 (77.8%)	0.081
Specialist asthma attendance	1359	432 (34.2%)	31 (32.6%)	0.759	27 (32.1%)	4 (36.4%)	0.779	4 (22.2%)	0.288
Asthma control worse during lockdown	1358	463 (36.7%)	50 (52.6%)	**0.002**	41 (48.8%)	9 (81.8%)	**0.039**	11 (61.1%)	**0.033**
Acute OCS course during lockdown	1363	433 (34.2%)	48 (50.0%)	**0.002**	40 (47.6%)	8 (66.7%)	0.217	13 (68.4%)	**0.002**
Hospital admission with COVID-19									
Admitted to hospital for COVID-19	97	0 (0.0%)	13 (1.4%)	–	0 (0.0%)	13 (100%)	<0.001	11 (57.9%)	–
Oxygen therapy	12	0 (0.0%)	7 (7.2%)	–	0 (0.0%)	7 (58.3%)	–	7 (36.8%)	–
ITU admission for COVID-19	12	0 (0.0%)	2 (2.1%)	–	0 (0.0%)	2 (15.4%)	–	1 (5.2%)	–
Chest radiograph suggestive of COVID-19	8	0 (0.0%)	7 (87.5%)	–	0 (0.0%)	7 (87.5%)	–	7 (87.5%)	–
Days in hospital[¶]	9	–	11 (5, 22)	–	–	11 (5,22)	–	11 (5,22)	–

Data are presented as n, mean±SD, n (%) or median (interquartile range), unless otherwise stated. BMI: body mass index; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; ICS: inhaled corticosteroids; BDP: budesonide dipropionate; OCS: oral corticosteroids; IL: interleukin; ITU: intensive therapy unit; –: no data to present. [#]: for confirmed COVID-19 *versus* no COVID-19; [¶]: data collected at registry entry; [+]: mepolizumab, benralizumab and reslizumab. Bold indicates statistical significance.

shielding advice (OR 0.40 (0.26-0.62), p<0.001 and OR 0.27 (0.16-0.45), p<0.001, respectively). In total, 44 (57%) patients with suspected and 8 (42%) patients with confirmed COVID-19 were infected before receiving shielding advice; 14 (77%) confirmed COVID-19 cases occurred in non-shielding households. Of those that shielded, 582 (47.0%) reported worsening of mental health. Although those with a history of depression/anxiety were particularly susceptible (OR 2.12 (1.35-3.33), p=0.001), 447 (76.8%) had no such premorbidity documented. Other characteristics associated with worsening mental health were female sex (OR 1.59 (1.19-2.13), p=0.001) and an elevated asthma control score (ACQ-6) ⩾1.5 (OR 1.80 (1.23-2.63), p=0.004). Younger patients (aged <40) were more affected than those >60 (OR 1.56 (1.08-2.33), p=0.020).

Of 1365 patients, 97 (7.1%) had confirmed/suspected COVID-19 and 19 (1.39%) had PCR/serology-confirmed infection; 13 (0.95%) were hospitalised with COVID-19. The median (interquartile range) hospital stay was 11 days (5, 22). A higher proportion of hospitalised *versus* ambulatory patients were non-Caucasian (25% *versus* 17.9%, p=0.053). Two patients died; both were Caucasian men aged over 65.

In total, 918 (67.5%) of patients were on a biologic and 735 (80%) of these on anti-IL-5/5R agents. No association was seen between biologics and risk of COVID-19 (OR 0.73 (0.46-1.14), p=0.165), but they were associated with better asthma control (OR 0.56 (0.41-0.77), p<0.001) and fewer exacerbations (OR 0.6 (0.44-0.83), p=0.002). There was no difference in the proportion of patients on biologic therapy between the mild and hospitalised COVID-19 groups (67.9% *versus* 61.5%, p=0.652). No association was seen between the type of biologic therapy and COVID-19. Maintenance OCS (mOCS) was not associated with COVID-19 (OR 1.18 (0.78-1.80), p=0.427); 35 (47.9%) ambulatory patients and 3 (23.0%) hospitalised patients were on mOCS (p=0.151).

A high dose of ICS (2000 µg beclometasone dipropionate (BDP) equivalent) was no different from a lower dose ICS (<1000 µg BDP equivalent) in its association with developing COVID-19 (OR 0.64 (0.32-1.31), p=0.234). However, hospitalised patients were on lower doses of ICS than ambulatory patients (median (interquartile range) BDP equivalent 1000 µg (800, 1600) *versus* 2000 µg (1600, 2000), p=0.002)), and a greater proportion had a history of poor adherence (53.8% *versus* 24.7%, p=0.033).

In summary, the majority of patients reported receiving and following shielding advice; 47% of shielding patients reported worsening of mental health, higher than the Office of National Statistics analysis of shielding patients in England (35%), with similar higher incidence in female and younger patients [6].

We found that monoclonal antibodies for asthma were not associated with increased risk of mild or severe COVID-19. This agrees with other emerging findings of low incidence of COVID-19 in the severe asthma population and biologics not affecting clinical outcome [7]. Poor asthma control increases the risk of severe viral exacerbations, so disease stability from biologics may be protective in itself [8].

Although numbers were small, there was an association seen with high-dose ICS and reduced hospitalisation from COVID-19. The Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial demonstrated that dexamethasone reduced mortality and progression to an intensive care unit in hospitalised patients [9]. *In vitro* studies have suggested ICS can reduce viral replication, whilst pretreatment with ICS has been shown to reduce the risk of acute respiratory distress syndrome in hospitalised patients [10, 11]. Further studies are required, but our findings support continued use of ICS at an appropriate dose for asthma control.

The strength of this study is the multicentre inclusion of well-characterised severe asthma patients. In addition to studying the impact of COVID-19 and effect of asthma medications, we enquired about the burden of shielding; a consideration when planning for the second wave. Limitations are the small number of patients hospitalised with COVID-19 preventing detailed analyses for risk factors. We also note that this study cannot separate out the risk of COVID-19 in an unshielded severe asthma population and that adherence to shielding was self-reported. Unfortunately, COVID-19 testing was not widely available in the early months of the pandemic; hence, despite including only patients reporting symptoms distinct from their usual asthma, the natural symptom overlap between poor asthma control and mild COVID-19 limits robust conclusions in the "suspected COVID-19" group.

In conclusion, hospitalisation and death occurred in small numbers of this UK severe asthma population. Adherence to shielding guidance may have contributed to this but led to worsening of mental health in our patients. Within our limited number of cases, biologic agents for asthma were not associated with increased risk of infection with the COVID-19 virus or hospitalisation.

Steven J. Smith[1], John Busby[2], Liam G. Heaney[2], Paul E. Pfeffer[3], David J. Jackson[4,5], Freda Yang[1], Stephen J. Fowler[6], Andrew Menzies-Gow[7], Elfatih Idris[8], Thomas Brown[9], Robin Gore[10], Shoaib Faruqi[11], Paddy Dennison[12], James W. Dodd[13], Simon Doe[14], Adel H. Mansur[15], Radhika Priyadarshi[3], Joshua Holmes[2], Andrew Hearn[4,5], Hamsa Al-Aqqad[6], Lola Loewenthal[7],

Angela Cooper[8], Lauren Fox[9], Mayurun Selvan[10], Michael G. Crooks[11], Alison Thompson[12], Daniel Higbee[13], Michelle Fawdon[14], Vishal Nathwani[15], LeanneJo Holmes[6] and Rekha Chaudhuri[1], on behalf of the UK Severe Asthma Registry

[1]Gartnavel General Hospital and University of Glasgow, Glasgow, UK. [2]Queen's University, Belfast, UK. [3]St Bartholomew's Hospital, Bart's Health NHS Trust, London & Queen Mary University of London, London, UK. [4]Guy's and St Thomas' Hospitals, London, UK. [5]Guy's and St Thomas' NHS Trust, London & King's College London, London, UK. [6]School of Biological Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester Academic Health Science Centre and NIHR Manchester Biomedical Research Centre, Manchester University Hospitals NHS Foundation Trust, Manchester, UK. [7]Royal Brompton Hospital, London, UK. [8]Royal Stoke University Hospital, Stoke, UK. [9]Queen Alexandra Hospital, Portsmouth, UK. [10]Addenbrooke's Hospital, Cambridge, UK. [11]Hull University Teaching Hospital, Hull, UK. [12]University Hospital Southampton, Southampton, UK. [13]Academic Respiratory Unit, University of Bristol and North Bristol Lung Centre, Southmead Hospital, Bristol, UK. [14]Royal Victoria Infirmary, Newcastle, UK. [15]Heartlands Hospital, University Hospitals Birmingham, Birmingham, UK.

Correspondence: Rekha Chaudhuri, Gartnavel General Hospital and University of Glasgow, Glasgow, UK, 1053 Great Western Road, Glasgow G12 0YN, UK. E-mail: rekha.chaudhuri@ggc.scot.nhs.uk

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Collaborators: Jayne Logan (Queen's University, Belfast, UK), Princy Kallukalam (Royal Stoke University Hospital, Stoke, UK), Olivia Darley (Royal Stoke University Hospital), Laura Wiffen (Queen Alexandra Hospital, Portsmouth, UK), Katherine Bunclark (Addenbrooke's Hospital, Cambridge, UK), Ciara Cashell (University Hospital Southampton, Southampton, UK), Jodie Hutchens (Royal Victoria Infirmary, Newcastle, UK) and Alison Scale (Royal Stoke University Hospital).

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