A call for more evidence documenting human-to-dog transmission of monkeypox virus

Sophie Seang and colleagues' description of human-to-dog transmission of monkeypox virus[1] raised concerns about the role of pets in monkeypox virus transmission, reinforcing recommendations from public health authorities that infected people should avoid contact with animals, isolate exposed pets, and consider removing exposed pets from the homes of immunocompromised people.[2] For example, the US Centers for Disease Control and Prevention now notes that human-to-dog transmission of monkeypox virus has occurred and that signs in dogs include development of a rash, "which to-date have been located on the abdomen and anus".[2]

However, the authors of this Correspondence provided insufficient evidence that the adult dog was infected with monkeypox virus: monkeypox virus was detected using PCR in scrapings from the dog's skin lesions and from swabs from its anus and oral cavity, but whether specimens were pooled or tested separately is not stated, and cycle threshold values were not provided to quantify the DNA present. The idea that this was contaminating DNA therefore remains plausible. The lesion on the dog's abdomen resembled a papule seen with bacterial folliculitis, and the anal lesion was barely perceptible. Biopsy proof that these lesions were pox lesions was absent, and there was no serological support for infection. In experimental infections of rabbits, mice, rats, guinea pigs, and hamsters, generalised skin lesions were documented only in rabbits, and adults were more resistant to disease than neonates.[3]

Although precautions are warranted until we know more, given the staggering implications of human-to-pet transmission, additional studies are required before concluding that dogs are susceptible to monkeypox virus infection and disease.

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1 Seang S, Burrel S, Todesco E, et al. Evidence of human-to-dog transmission of monkeypox virus. *Lancet* 2022; **400:** 658–59.

2 Centers for Disease Control and Prevention. Monkeypox: pets in the home. Aug 17, 2022. https://www.cdc.gov/poxvirus/monkeypox/specific-settings/pets-in-homes.html (accessed Aug 23, 2022).

3 Marennikova SS, Seluhina EM. Susceptibility of some rodent species to monkeypox virus, and course of the infection. *Bull World Health Organ* 1976; **53:** 13–20.

Characterising adults in Scotland who are not vaccinated against COVID-19

By Aug 10, 2022, 3 497 208 of the estimated 4·4 million adults living in Scotland had received three doses of a COVID-19 vaccine. However, a proportion of the adult population remains unvaccinated (defined as no record of any vaccine being administered) and susceptible to severe COVID-19 outcomes. Characterising this population can help to understand gaps in vaccine coverage and determinants of vaccine hesitancy and could support targeted public health messaging. Unlike the vaccinated population, on whom information is gathered at the point of vaccination, current estimates of the unvaccinated population are calculated using general practitioner (GP) records. However, complications arise because GP records can include people who have moved away from Scotland; estimates suggest that GP records contain a population 8% greater than National Records of Scotland population estimates.[1]

We used data from linked national health records to estimate the number and describe the characteristics of adults living in Scotland for whom there is no record of any COVID-19 vaccination. This analysis was conducted using the Early Pandemic Evaluation and Enhanced Surveillance of COVID-19 (EAVE II) platform,[2] a national COVID-19 surveillance platform using anonymised individual patient-level records from all 940 general practices in Scotland, deterministically linked to multiple datasets recording morbidity, mortality, virology, vaccination, and prescribing (appendix p 1). Linkage was done with a unique identifier for each resident in Scotland who is registered with a GP.

The EAVE II cohort includes all individuals registered with a GP in Scotland as of March 1, 2020, including those who have subsequently left Scotland without informing their GP. To exclude people no longer living in Scotland, we defined unvaccinated individuals as those without COVID-19 vaccination records who had at least one interaction with the National Health Service (NHS) Scotland since Jan 1, 2019. We used the EAVE II cohort at a cutoff date of Dec 8, 2020 (the start of the UK's vaccination programme). In the appendix (p 2) we outline the process of identifying the unvaccinated population. We excluded individuals who died of any cause before the cutoff date and those recorded as having left Scotland. As individuals younger than 18 years were only invited for vaccination more recently (between August, 2021, and March, 2022, depending on age), our analysis was restricted to adults aged 18 years and older.

This identification process yielded 4 712 810 individuals who were recorded as eligible for COVID-19 vaccination. Linkage of vaccine eligibility data with COVID-19 vaccination records identified 842 029 (17·9%) of the 4 712 810 eligible individuals as having no record of vaccination. Among these 842 029 people, 86 489 (10·3%) had documented reasons for not receiving a vaccine, including immunisation con-

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For **Scotland's COVID-19 vaccine dashboard** see https://public.tableau.com/app/profile/phs.covid.19/viz/COVID-19DailyDashboard_15960160643010/Overview

traindicated, immunisation consent not indicated, reason for non-vaccination, generally unwell, and vaccine refused by patient.[3] Immunisation contraindicated was recorded for nearly one fifth of all unvaccinated individuals for whom a reason was documented. Laboratory records identified 254 049 individuals with no vaccination record who were tested at least once for SARS-CoV-2 by RT-PCR since the start of the pandemic. Non-hospital-based prescription records identified 416 499 individuals with no vaccination record who had been prescribed medication of any description since Jan 1, 2019. 285 647 unvaccinated individuals had interacted with the unscheduled care pathway (one or more of NHS 24, out-of-hours GP consultations, or the Scottish Ambulance Service), while 133 569 people with no vaccination record had at least one hospital admission according to the Scottish Morbidity Records. In total, 268 740 individuals with no evidence of vaccination were identified in any of the above data sources.

573 289 eligible individuals aged 18 years or older were identified as having no record of any COVID-19 vaccination in Scotland and at least one contact with NHS Scotland since Jan 1, 2019. We then excluded people who had died since the start of the vaccination programme, and those for whom immunisation contraindicated was recorded as the reason for non-vaccination. On Aug 10, 2022, our method identified 494 288 individuals with no record of any COVID-19 vaccination.

This unvaccinated cohort contained similar proportions of males and females, with similar age distribution across both sexes (appendix pp 3–4). The mean age was 42·4 years. Most unvaccinated people lived in urban settings, and 143 558 (29·0%) of 494 288 unvaccinated individuals—compared with 719 251 (18·7%) of 3 847 789 vaccinated individuals—resided in areas ranked by the Scottish Index of Multiple Deprivation as containing the most deprived 20% of the Scottish population.

On the basis of GP records, the majority (298 866, 60·5%) of 494 288 unvaccinated individuals were not known to have any comorbidities, compared with 1 988 751 (51·7%) of 3 847 789 vaccinated individuals, whereas 55 122 (11·2%) of 494 288 unvaccinated individuals were recorded as having three or more comorbidities, compared with 481 019 (12·5%) of 3 847 789 vaccinated individuals. The most frequently reported comorbidities among 494 288 unvaccinated individuals were chronic respiratory disease (77 643, 15·7%), depression (63 375, 12·8%), and hypertension (52 474, 10·6%).

One in five (103 505, 20·9%) of 494 288 unvaccinated individuals were prescribed medications for conditions relating to the CNS, compared with 655 531 (17·0%) of 3 847 789 vaccinated individuals, with more than a third of this unvaccinated group (40 179 [38·8%] of 103 505) prescribed antidepressants.

Multivariable logistic regression modelling was used to identify the factors most likely to predict COVID-19 vaccination. Male sex, high deprivation, living in large urban areas, being prescribed medication for CNS disorders, and having more than three comorbidities were most associated with unvaccinated status, although individuals with some comorbidities—such as hypertension, diabetes, and chronic respiratory disease—were more likely to be vaccinated.

Previous UK data have reported on inequalities of COVID-19 vaccination coverage, with considerably lower uptake among some groups.[4] Notably, although increasing age and presence of comorbidities are among the most widely recognised risk factors for COVID-19 mortality,[5–7] people with a substantial number of comorbidities remained at increased risk of being unvaccinated.

The limitations of our approach include a lack of ethnicity data, which are important because variations in vaccine uptake among different ethnic groups are known.[8] Additionally, although our approach minimises false inflation of the number of unvaccinated people, some of these individuals will have had no recent interaction with the health-care system and so will remain undetected. Unvaccinated people might also be less likely to have health-seeking behaviour, reducing the chance of them being detected through this method.[9] Some individuals might have been vaccinated outside of Scotland, which was not captured in our analysis. Identifying people vaccinated in other countries will improve future estimates of unvaccinated populations.

In summary, this national analysis revealed that, even after accounting for possible overinflation of population size, a considerable proportion of the adult population of Scotland remains unvaccinated against COVID-19. We also identified predictors of unvaccinated status, which can help with formulating a revised national vaccination strategy.

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1 Stockton D. PHS reporting of cases, hospitalisations and deaths from COVID-19 by vaccine status—interpreting the data. Jan 19, 2022. https://publichealthscotland.scot/our-blog/2022/january/phs-reporting-of-cases-hospitalisations-and-deaths-from-covid-19-by-vaccine-status-interpreting-the-data/ (accessed March 22, 2022).
2 Simpson CR, Robertson C, Vasileiou E, et al. Early pandemic evaluation and enhanced surveillance of COVID-19 (EAVE II): protocol for an observational study using linked Scottish national data. *BMJ Open* 2020; **10:** e039097.
3 UK Health Security Agency. COVID-19: the green book, chapter 14a. Nov 27, 2020. https://www.gov.uk/government/publications/covid-19-the-green-book-chapter-14a (accessed Aug 11, 2022).
4 Perry M, Akbari A, Cottrell S, et al. Inequalities in coverage of COVID-19 vaccination: a population register based cross-sectional study in Wales, UK. *Vaccine* 2021; **39:** 6256–61.
5 Flook M, Jackson C, Vasileiou E, et al. Informing the public health response to COVID-19: a systematic review of risk factors for disease, severity, and mortality. *BMC Infect Dis* 2021; **21:** 342.
6 Parohan M, Yaghoubi S, Seraji A, Javanbakht MH, Sarraf P, Djalali M. Risk factors for mortality in patients with coronavirus disease 2019 (COVID-19) infection: a systematic review and meta-analysis of observational studies. *Aging Male* 2020; **23:** 1416–24.
7 Booth A, Reed AB, Ponzo S, et al. Population risk factors for severe disease and mortality in COVID-19: a global systematic review and meta-analysis. *PLoS One* 2021; **16:** e0247461.
8 Gaughan C, Razieh C, Khunti K, et al. COVID-19 vaccination uptake amongst ethnic minority communities in England: a linked study exploring the drivers of differential vaccination rates. *J Public Health* 2022; fdab400.
9 Glasziou P, McCaffery K, Cvejic E, et al. Testing behaviour may bias observational studies of vaccine effectiveness. *J Assoc Med Microbiol Infect Dis Can* 2022; published online July 12. https://doi.org/10.3138/jammi-2022-0002.

Maintenance antipsychotic trials and the effect of withdrawal

Johannes Schneider-Thoma and colleagues[1] report the results of a systematic review and network meta-analysis of antipsychotics for the maintenance treatment of adults with schizophrenia, but did not consider the effect of withdrawal-related effects when interpreting their results. They included 49 trials with a placebo group, of which we were able to access information on participants and design for 47 trials (appendix). Of those 47 trials, all used a discontinuation design, most involving people who had been taking antipsychotics for many years, and 43 trials described or implied abrupt cessation of antipsychotic treatment upon assignment to placebo, although the trial with the longest taper period stopped antipsychotics over 4–6 weeks. These rapid stopping schedules, including of depot formulations, are likely to induce somatic and psychiatric withdrawal effects (eg, anxiety), which are now established symptoms, as recently shown in an individual participant data meta-analysis.[2] Withdrawal effects could be conflated with worsening of the illness and therefore interpreted as relapse,[3,4] inflating the apparent relapse rate in the placebo group. Withdrawal might also have a destabilising effect on the illness leading to relapse, and abrupt cessation of antipsychotics could outright induce psychotic symptoms.[4] Therefore, the placebo-controlled discontinuation trials included by Schneider-Thoma and colleagues[1] do not inform about potential benefits of starting maintenance treatment with antipsychotics to begin with, and provide misleading information on the benefits and harms of continuing versus stopping ongoing antipsychotic treatment, by ignoring the consequences of withdrawal effects.[4]

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1 Schneider-Thoma J, Chalkou K, Dörries C, et al. Comparative efficacy and tolerability of 32 oral and long-acting injectable antipsychotics for the maintenance treatment of adults with schizophrenia: a systematic review and network meta-analysis. *Lancet* 2022; **399:** 824–36.
2 Brandt L, Schneider-Thoma J, Siafis S, et al. Adverse events after antipsychotic discontinuation: an individual participant data meta-analysis. *Lancet Psychiatry* 2022; **9:** 232–42.
3 Horowitz MA, Jauhar S, Natesan S, Murray RM, Taylor D. A method for tapering antipsychotic treatment that may minimize the risk of relapse. *Schizophr Bull* 2021; **47:** 1116–29.
4 Moncrieff J. Antipsychotic maintenance treatment: time to rethink? *PLoS Med* 2015; **12:** e1001861.

See **Online** for appendix

Authors' reply

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