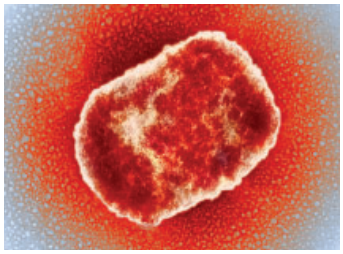
research

Risk prediction of falls in patients using antihypertensives
p 267



Serial interval and incubation period of monkeypox in the UK
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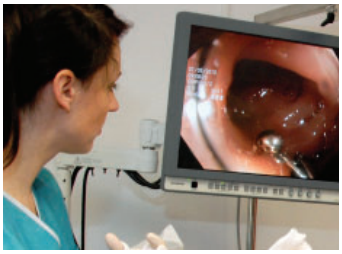

Polygenic risk scores and risk of colorectal cancer
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ORIGINAL RESEARCH Retrospective cohort study

Development and external validation of a risk prediction model for falls in patients with an indication for antihypertensive treatment

Archer L, Koshiaris C, Lay-Flurrie S, et al; on behalf of the STRAtifying Treatments In the multi-morbid Frail elderlY (STRATIFY) investigators

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Study question Can a clinical prediction model be developed to accurately identify patients with an indication for hypertensive treatment who are at risk of hospital admission or death from a fall?

Methods Retrospective cohort designs were used to develop and externally validate the STRATIFY-Falls clinical prediction model, using two separate sets of UK primary care data from electronic health records contained within the Clinical Practice Research Datalink (CPRD). Model development was conducted in data from CPRD GOLD, using a competing risk model to account for the risk of death from other causes. External validation was conducted using data from CPRD Aurum.

Study answer and limitations The final model consisted of 24 predictors, including a history of falls, multiple sclerosis, heavy alcohol consumption, high deprivation score, and prescribed drugs, which were all strong predictors of subsequent serious falls, conditional on the other model variables. Upon external validation, the model discriminated well between patients who went on to have a serious fall and those who did not (C statistic at 10 years 0.83, 95% confidence interval 0.83 to 0.84), but calibration indicated under-prediction of risk, particularly in those at higher risk of serious falls (observed to expected ratio at 10 years 1.84, 95% confidence interval 1.81 to 1.87). It is possible that some of the fall events were not reported or captured correctly within the electronic health record, therefore potentially underestimating the incidence of falls, which could have affected the performance of the model.

What this study adds Despite miscalibration, analyses suggest the model has clinical utility and so may be useful for identifying patients with a high risk of falls, who may benefit from closer monitoring or early intervention, such as deprescribing.

Funding, competing interests, and data sharing
Authors had financial support from the Wellcome Trust, Royal Society, and National Institute for Health and Care Research for the submitted work. No other competing interests declared.

Data were obtained via a CPRD institutional licence.

Requests for data sharing should be made directly to the CPRD. The algorithm is freely available for research use and can be downloaded from https://process.innovation.ox.ac.uk/software/.

Predictive performance statistics of falls prediction models on external validation in CPRD Aurum

	Recalibrated model	
Model performance statistics	**5 years**	**10 years**
Observed to expected ratio (95% CI)	1.906 (1.874 to 1.939)	1.839 (1.811 to 1.865)
C statistic (95% CI)	0.843 (0.841 to 0.844)	0.833 (0.831 to 0.835)
D statistic (95% CI)	1.894 (1.746 to 2.042)	1.597 (1.472 to 1.721)
Mean (SD) Royston and Sauerbrei's R^2	47.7 (0.07)	39.4 (0.07)

CI=confidence interval; SD=standard deviation.

The dynamics of monkeypox transmission

ORIGINAL RESEARCH: SPECIAL PAPER Contact tracing study

FAST TRACK

Transmission dynamics of monkeypox in the United Kingdom

Ward T, Christie R, Paton RS, Cumming F, Overton CE

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Study question What are the transmission dynamics of the 2022 monkeypox outbreak in the United Kingdom?

Methods Information from individuals who tested positive for monkeypox virus using polymerase chain reaction in the UK between 6 May and 1 August 2022 were linked to their contacts through contact tracing case questionnaires. The main outcome measures were serial interval (time from symptom onset in the case patient to symptom onset in the contact) and incubation period (time from exposure to onset of symptoms). Analyses were performed using two bayesian time delay models: one corrected for interval censoring (ICC) and one corrected for interval censoring, right truncation, and epidemic phase bias (ICRTC). Growth rates of cases by reporting date, when monkeypox virus was confirmed and reported to the UK Health Security Agency, were estimated using generalised additive models.

Study answers and limitations The study sample comprised 2746 people with polymerase chain reaction confirmed monkeypox virus. The estimated mean incubation period of infection was 7.6 days (95% credible interval 6.5 to 9.9) using the ICC model and 7.8 days (6.6 to 9.2) using the ICRTC model. The estimated mean serial interval was 8.0 days (95% credible interval 6.5 to 9.8) using the ICC model and 9.5 days (7.4 to 12.3) using the ICRTC model. For both models, the median serial interval was shorter than the median incubation period, suggesting substantial pre-symptomatic transmission. Depending on the model, the median serial interval was between 0.3 and 1.7 days shorter than the incubation period. For linked patients, 10 out of 13 showed pre-symptomatic transmission. Cases doubled every 9.07 days (95% confidence interval 12.63 to 5.08) at the start of the epidemic but halved every 29 days (95% confidence interval 38.02 to 23.44) on 1 August.

COMMENTARY Pre-exposure vaccination and vaccine equity are urgently needed worldwide

After a surge of monkeypox infections starting in May 2022, 99% from countries without previous known endemic spread—by the end of August 2022, new infections started to trend downward.[1 2] Whether this marks the end of the outbreak or whether intermittent surges will continue is not yet clear. Understanding the underlying transmission dynamics is key to shedding light on this, as well as informing future interventions.

In their study, Ward and colleagues used routine case questionnaires and contact tracing data to estimate two important characteristics of the monkeypox outbreak in the UK: the serial interval and incubation period.[3] They found that shorter serial intervals are more common than shorter incubation periods. One explanation the authors provided is that considerable transmission is occurring before the appearance or detection of symptoms; otherwise, the serial interval should at a minimum equal the incubation period.

This study had a relatively large sample size and appropriate statistical adjustments to account for key biases in the data. The researchers used paired case-contact data to validate their model based conclusions. One limitation was the use of patient reported variables, with the potential for recall and response biases, which is particularly critical for the date of symptom onset. Contact tracing could also be a source of bias. For example, in the case of monkeypox infection after a superspreading event in which the index case was not identified, the serial interval could be underestimated.[4]

Pre-symptomatic transmission

Other studies have also hinted at pre-symptomatic transmission. Anal swabs collected from 213 asymptomatic men who have sex with other men were retrospectively screened for monkeypox virus; 13 tested positive on polymerase chain reaction (PCR) and two subsequently developed symptoms.[5] Although a positive PCR test result does not necessarily indicate that an individual is infectious, this study raised questions about transmission being dependent on symptoms.

Vaccination is likely to be more cost effective than managing the consequences of preventable infections

Evidence supporting pre-symptomatic transmission is not definitive, but if Ward and colleagues' findings are supported by those of other studies, then pre-symptomatic transmission, or transmission before symptoms are detected, would have important implications for infection control globally. Specifically, postexposure or "ring" vaccination of contacts identified only through individuals with symptoms, could be inadequate.[5 6] In the US and UK, vaccination campaigns have already shifted from exclusively postexposure prophylaxis to include pre-exposure prophylaxis for some high risk groups.[7 8]

Vaccine equity

Equitable access to vaccines is critical to monkeypox control efforts globally, and lack of access is a serious concern, particularly if pre-symptomatic transmission is occurring. Currently, Jynneos (also known as Imvanex), which is in limited supply, is the primary vaccine in use for monkeypox in the US, Canada, Europe, and the UK[9 10]; the older smallpox vaccine ACAM2000 is less commonly used and only in select patients.[11]

From the patient perspective, monkeypox infection can be extremely painful and isolating, greatly affecting psychological wellbeing.[12 13] High risk communities are keen to access vaccination, as evidenced by long vaccination queues.[14 15]

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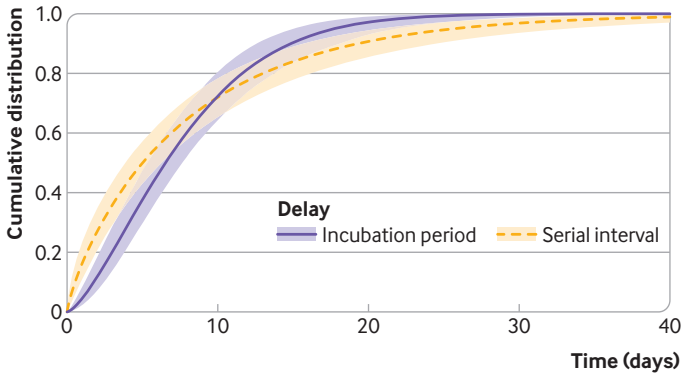
The main limitations are relying on contact tracing to identify the correct case-contact pairs and the self-reported data on date of symptom onset.

What this study adds Short serial intervals were more common than short incubation periods, validated through linked patient level records, and suggested considerable pre-symptomatic transmission of monkeypox. For patients who could be linked through personally identifiable data, four days was the maximum time that transmission was detected before symptoms manifested. An isolation period of 16 to 23 days would be required to detect 95% of people with a potential infection. The 95th centile of the serial interval was between 23 and 41 days, suggesting long infectious periods.

Funding, competing interests, and data sharing The authors were employed by the UK Health Security Agency but received no specific funding for this study. No competing interests declared. Data requests can be made to the Office for Data Release (www.gov.uk/government/publications/accessing-ukhsa-protected-data/accessing-ukhsa-protected-data) and by contacting DataAccess@ukhsa.gov.uk. Requests are reviewed by the Office for Data Release and subject to strict confidentiality provisions.



Cumulative distribution function of the serial interval and incubation period for monkeypox using the ICRTC (interval censoring right truncation corrected) model fit to a gamma distribution for the serial interval and a Weibull distribution for the incubation period with 95% credible intervals

Ensuring that effective vaccines are available to all communities and individuals at risk should be a priority for health leaders in affected countries, and for global health leaders more broadly.

In the US, for example, black people account for 50% of monkeypox infections but received only 12% of the vaccines.[16 17] In Nigeria, where monkeypox is endemic, vaccines are currently unavailable so no vaccination policy of any kind can be implemented, an inequity reminiscent of the covid-19 pandemic.[18 19] This is also the case for many other African countries.

From a health system perspective, vaccination is likely to be more cost effective than managing the consequences of preventable infections, including hospital admissions, loss of income during isolation, and long term complications. These costs put extra pressure on health systems in low income countries that already have a high burden of infectious diseases.

Public health measures that have been critical during monkeypox outbreaks in high income countries, such as PCR testing and vaccination, remain unavailable in much of Africa.[9] In their study, Ward and colleagues from the UK Health Security Agency relied on resource intensive contact tracing and case questionnaires—approaches that are under-supported in low resource countries where monkeypox is endemic.

As the monkeypox outbreak declines in Europe and North America, we have a responsibility to deploy effective tools for viral control on a global level—not just in wealthy nations. These tools include research into understanding transmission dynamics in African settings and the inclusion of endemic countries in vaccine trials.

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ANP/ALAMY

Integrating genome-wide polygenic risk scores and non-genetic risk to predict colorectal cancer diagnosis

Briggs SEW, Law P, East JE, et al

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Study question Does combining polygenic risk scores with the QCancer-10 (colorectal cancer) prediction model for non-genetic risk improve identification of people at highest risk of colorectal cancer?

Methods This study identified the best polygenic risk scores for colorectal cancer, combined this with QCancer-10, and compared its performance with QCancer-10 alone in 434 587 individuals aged 40-69 years from the UK Biobank study with complete genetic and QCancer-10 predictor data. The primary outcome was prediction of colorectal cancer diagnosis by genetic, non-genetic, and combined risk models through use of self-reported data, linked cancer and death registry data, and hospital data.

Study answer and limitations Polygenic risk scores developed using the LDpred2 program performed best across all metrics (odds ratio per standard deviation 1.584 (95% confidence interval 1.536 to 1.633)). Integrated models of QCancer-10 plus polygenic risk scores outperformed QCancer-10 alone across all metrics, although differences were modest. For example, the integrated LDpred2 model produced a C statistic of 0.730 (95% confidence interval 0.720 to 0.741), compared with 0.693 (0.682 to 0.704) in QCancer-10 alone in men, with similar differences seen in women. In the top 20% of individuals at highest absolute risk, the sensitivity of integrated LDpred2 models for predicting a diagnosis of colorectal cancer was 47.8% in men and 42.7% in women, and the specificity was 80.3% in men and 80.1% in women. Illustrative decision curve analysis indicated a small improvement in net benefit with models for QCancer-10 plus polygenic risk scores compared with QCancer-10 alone. Limitations of the study include the healthy volunteer bias of the data from the UK Biobank study and under-representation of minority ethnic groups in the modelling cohort.

What this study adds Integrating polygenic risk scores with QCancer-10 modestly improves risk prediction over use of QCancer-10 alone. Given that QCancer-10 data can be obtained relatively easily from health records, and gains from adding polygenic risk scores are modest, use of these scores currently has no clear justification in risk stratified population screening for colorectal cancer.

Funding, competing interests, and data sharing Supported by research grants from the Medical Research Council, Cancer Research UK, Wellcome Trust, and National Institute for Health and Care Research Oxford Biomedical Research Centre. Model specifications will be deposited in the polygenic risk score catalogue repository.

Apparent and internally validated performance of QCancer-10 risk score with LDpred2 sparse grid polygenic risk score model (QCancer-10+LDP) and QCancer-10 plus genome-wide association studies significant polygenic risk score (QCancer-10+GWS) model, compared with external validation of QCancer-10 in the same participants. Values are performance indices (95% confidence intervals) unless otherwise specified

	QCancer-10+LDP		QCancer-10+GWS		
	Apparent	Internal validation	Apparent	Internal validation	QCancer-10
Men					
Harrell's C statistic	0.730 (0.720 to 0.741)	0.730	0.715 (0.706 to 0.726)	0.715	0.693 (0.682 to 0.704)
Dxy	0.460 (0.440 to 0.481)	0.459	0.430 (0.411 to 0.452)	0.430	0.847 (0.841 to 0.852)
Royston's D statistic	1.283 (1.224 to 1.342)	1.280	1.201 (1.148 to 1.259)	1.119	1.058 (0.987 to 1.121)
R^2_D (%)	28.2 (26.3 to 30.1)	28.1	25.6 (23.9 to 27.5)	25.6	21.1 (18.9 to 23.1)
Scaled Brier (%)	0.82	0.81	0.79	0.78	0.59
Calibration slope	NA	0.998	NA	0.998	0.995 (0.914 to 1.063)
Women					
Harrell's C statistic	0.687 (0.673 to 0.702)	0.686	0.669 (0.655 to 0.683)	0.668	0.645 (0.631 to 0.659)
Dxy	0.374 (0.347 to 0.404)	0.372	0.338 (0.310 to 0.367)	0.337	0.822 (0.816 to 0.830)
Royston's D statistic	1.056 (0.983 to 1.141)	1.055	0.926 (0.852 to 1.002)	0.925	0.769 (0.695 to 0.847)
R^2_D (%)	21.0 (18.7 to 23.7)	21.0	17.0 (14.8 to 19.3)	17.0	12.4 (10.3 to 14.6)
Scaled Brier (%)	0.34	0.34	0.28	0.28	0.20
Calibration slope	NA	0.996	NA	0.996	0.805 (0.724 to 0.899)

Pairwise comparisons of performance metrics were all significantly different P<0.001. Dxy=Somers' D_{xy} rank correlation; R^2_D=Royston and Sauerbrei's R^2_D (explained variation); NA=not available.