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#### A large multi-country outbreak of monkeypox across 41 countries in the WHO European Region, 7 March to 23 August 2022

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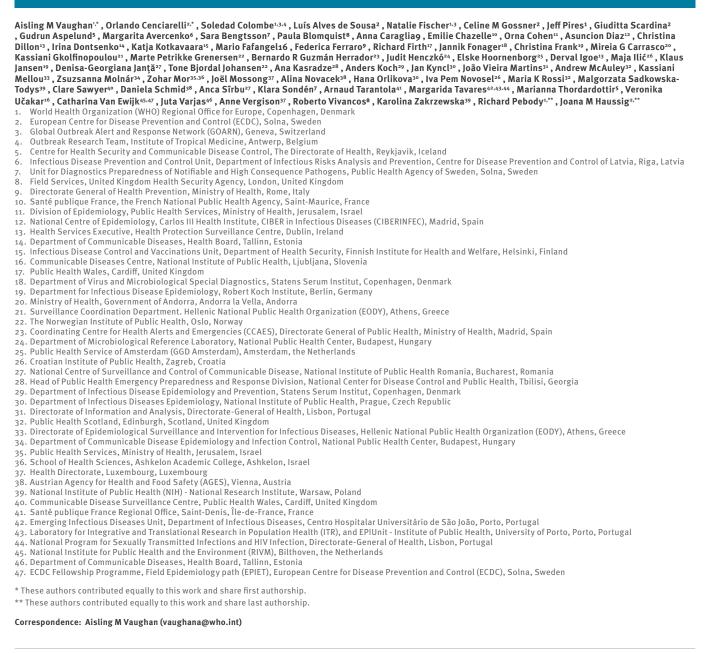
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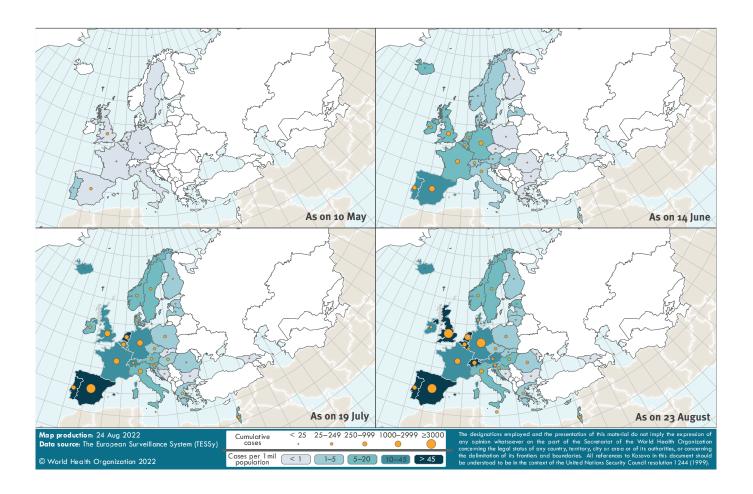
Following the report of a non-travel-associated cluster of monkeypox cases by the United Kingdom in May 2022, 41 countries across the WHO European Region have reported 21,098 cases and two deaths by 23 August 2022. Nowcasting suggests a plateauing in case notifications. Most cases (97%) are MSM, with atypical rash-illness presentation. Spread is

#### mainly through close contact during sexual activities. Few cases are reported among women and children. Targeted interventions of at-risk groups are needed to stop further transmission.

Since detection of monkeypox virus (MPXV) transmission outside endemic areas in May 2022, a large

#### FIGURE 1

Geographical distribution of monkeypox cases reported through The European Surveillance System (TESSy) by 36 WHO European Region countries, 7 March–23 August 2022 (n = 20,690 cases)



Distribution of cases by symptom onset or, if missing, the earliest date of diagnosis or notification.

multi-country monkeypox (MPX) outbreak has been ongoing worldwide, with 42,807 cases and 12 deaths reported in 97 Member States across six World Health Organization (WHO) Regions by 23 August 2022 [1]. On 23 July, the WHO Director General declared this outbreak a public health emergency of international concern (PHEIC) [2]. Here we describe the epidemiological features of MPX and analyse disease severity as well as the effect of prior smallpox vaccination on all cases in the WHO European Region reported in TESSy up to 23 August 2022 to inform optimal public health responses.

#### Epidemiological situation in the WHO European Region

On 13 May 2022, the United Kingdom (UK) reported a non-travel-associated family cluster of MPX cases to the WHO through International Health Regulations (IHR) mechanisms [3]. Thereafter, the UK and other countries, including Portugal, Sweden, Belgium, Germany, Spain, France, Italy, the Netherland, Austria (chronological order) began detecting and reporting MPX cases of Clade II (formerly West African clade) [3,4], primarily among men who have sex with men (MSM). Subsequent retrospective testing of a residual sample in the UK dated the earliest known case back to 7 March 2022. Until end of July [1], Europe remained the epicentre of this large and geographically widespread outbreak, with a steady increase of cases and affected countries (Figure 1).

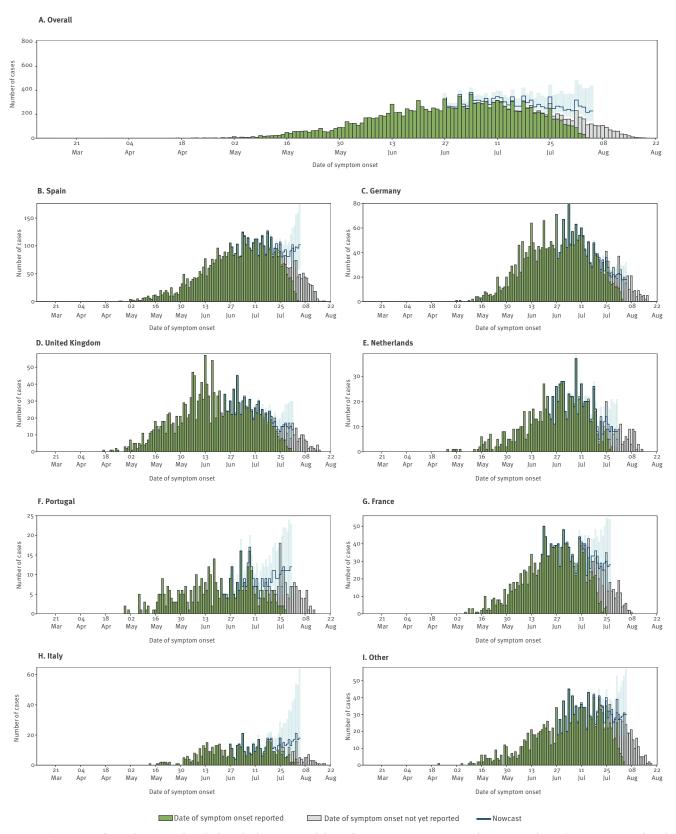
Of 21,098 cases reported in the WHO European Region, case-based data for 20,690 cases (98.1%) from 36 of 41 countries were reported to the European Centre for Disease Prevention and Control (ECDC) and the WHO Regional Office for Europe, through The European Surveillance System (TESSy), using national (n = 9,831 cases) or WHO/ECDC case definitions (n = 1,314 cases) [5,6]. Information is missing or unknown for the other 9,545 cases. Of the total, 99.3% (20,545/20,690) were laboratory-confirmed.

## Nowcasting of monkeypox cases reported in the WHO European Region

To assess the current epidemiological situation, we performed nowcasting on TESSy case-based data [7],

#### FIGURE 2

Distribution of reported and nowcasted cases of monkeypox by date of onset of symptoms, 36 WHO European Region countries in order of decreasing incidence, 7 March (week 10)–23 August (week 34) 2022



Nowcasting was performed up to 17 days before the last reported date of symptom onset. Reported cases are shown in green. Cases for which the date of symptom onset is not yet in the notification system at the time of nowcasting are shown in grey. Nowcasting point estimate (line) and 95% confidence interval (shaded area) are shown in blue.

Other reporting countries: Andorra, Austria, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, Czechia, Denmark, Estonia, Finland, Georgia, Greece, Hungary, Iceland, Ireland, Israel, Latvia, Lithuania, Luxembourg, Malta, Norway, Poland, Republic of Moldova, Romania, Slovakia, Slovenia, Sweden, Switzerland.

with a prior negative binomial distribution (mean: 7 days and overdispersion 1.6 days) to adjust for reporting delay, and right truncation at 17 days, which corresponds to 95<sup>th</sup> percentile of reporting delay for cases in the last weeks. The median reporting delay, defined as the difference in days from date of symptom onset to date of notification at national level, was 7 days (range: 1–117 days) for 17,101 (82.6%) cases with complete date variables. Nowcast estimates suggest that the regional epidemic trend is plateauing overall, with some intercountry differences emerging (Figure 2).

# Demographic characteristics, clinical presentation and outcome

Most cases (98.8%; 17,685/17,896) identified as male, and the median age of all cases was 37 years (interquartile range (IQR): 31–44; range: 0–88 years) and 37.2% (3,070/8,257) were HIV-positive (Table 1). Among male cases, 96.9% (8,771/9,053) self-identified as MSM. A small proportion of infections have consistently been reported in women and children. In total, 220 adult cases with a known gender were reported to be non-male (1.2%) and 41 cases aged under 18 years (0.2%) have been reported in TESSy. Of these, 15 cases were under 15 years of age.

Of those reporting symptoms, most reported rash (95.0%; 12,415/13,072) and at least one systemic symptom (64.8%; 8,476/13,072) such as fever, fatigue, muscle pain, chills or headache. Some cases (48.1%; 5,973/12,415 reported rash in the anogenital region; of those, 554 reported no other symptom. Six percent of cases (576/9,732) were hospitalised (n = 129 for isolation purposes; n = 197 for clinical care and n = 250 for unknown reasons). Cases hospitalised for isolation purposes were considered as 'not hospitalised' in the analyses. Three cases were admitted to an intensive care unit (ICU) and two of these cases died with encephalitis.

To estimate predictors of severity, case hospitalisation ratios were calculated. The overall case hospitalisation ratio was 10 per 1,000 cases (Table 1) and did not vary over time (data not shown). Younger cases, those presenting with lymphadenopathy and those without systemic symptoms were at significantly higher risk of hospitalisation (p=0.015, p=0.005 and p<0.001, respectively). However, surveillance data does not allow capture of the full clinical course, therefore lack of systemic symptoms at the time of report cannot be interpreted as a predictor of severe disease without further in-depth clinical characterisation. No statistically significant difference was observed for other variables. Firth logistic regressions with hospitalisation as a binary outcome and age as a linear variable showed decreasing odds of hospitalisation with increasing age (odds ratio (OR): 0.97; 95% confidence interval (CI): 0.96-0.99). When considering those hospitalised for unknown reasons, HIV-positive cases were at higher risk of hospitalisation compared with HIV-negative

cases (46 and 30/1,000 respectively, p<0.001) (data not shown).

#### **Exposure settings and transmission routes**

Detailed data on possible exposure in the 21 days before symptom onset was only available for a minority of cases, limited to some countries. Sexual contact was reported as a possible route of transmission in 93.9% (6,385/6,797) of cases, followed by other person-to-person routes (PTP; non-sexual, non-mother-tochild and non-healthcare associated, 5.3%; 359/6,797) or fomites (0.2%; 11/6,797) (Table 2). Of the cases who reported 'other' as a route (0.3%; 41/6,797), 12 also reported likely exposure at a bar event, and one reported household fomite transmission. Many cases reported exposure at a private party/club (69.4%; 2,530/3,643) and/or a large event (28.3%; 1,030/3,643). Household exposure was reported by 233 (6.4%) cases, and these cases also reported sexual transmission (78.1%; 153/196) or PTP (21.4%; 42/196). Likely modeof-transmission and exposure setting was reported for five cases under 15 years, which indicated transmission through contact with a parent or in the household.

Sixty-four cases were health workers (1.7%; 64/3,708); of these 62 (96.9%) were male and 55 (85.9%) were MSM. While no occupational exposure in the health-care setting or workplace has been reported through TESSy, three instances of occupational exposure have been reported to the WHO through other routes to date. Other modes of transmission, including zoonotic, vertical and laboratory transmission were not reported for any cases. Possible exposure settings and transmission routes are not mutually exclusive and local outbreak investigations will help identify clear transmission pathways.

### Smallpox vaccination and disease severity

Only 16.8% (3,525/20,960) of cases reported on smallpox vaccination. Of these, most (81.8%; 2,577/3,152) self-reported as both unvaccinated prior to this outbreak and for this outbreak (median age: 36 years; IQR: 30-41), 423 reported receiving a vaccination before this outbreak (median age: 50 years; IQR: 39-56), one reported primary preventive (pre-exposure) vaccination (PPV) (aged 28 years) and 42 reported postexposure preventative vaccination (PEPV) for this event (median age: 35.5 years; IQR: 30.3–43.8). We assessed the potential effect of prior smallpox vaccination on disease severity and hospitalisation (Table 3). Overall, 197 cases were hospitalised for clinical care, of which 12 cases (11.3%) reported prior vaccination. Firth logistic regressions to assess association between hospitalisation and vaccination were not statistically significant (adjusted OR: 1.07; 95% CI: 0.53–1.97) (Table 3).

#### Discussion

The MPXV is currently the most prevalent cause of orthopoxvirus infection in humans. MPX outbreaks have previously occurred largely in African countries, where the virus is enzoonotic. However, in recent

#### TABLE 1

Demographic, clinical characteristics and disease-severity of confirmed and probable monkeypox cases, 36 WHO European Region countries, 7 March–23 August 2022, (n=20,690 cases)

Variables		Overall	cases	Hospitalised		No hospita		Unknown		Hospitalisation ratio	
			%		%		%		%	(per 1,000 cases)	p value
Total cases		20,690	100	197	100	10,601	100	9,892	100	10	
	0-17	41	0.2	2	1.0	25	0.2	14	0.1	49	
	18-30	5,078	24.5	57	28.9	2,504	23.6	2,517	25.4	11	
	31-40	8,231	39.8	87	44.2	4,202	39.6	3,942	39.9	11	
Age group (years)	41-50	4,970	24.0	40	20.3	2,695	25.4	2,235	22.6	8	0.015
	51-60	1,882	9.1	9	4.6	947	8.9	926	9.4	5	
	> 60	442	2.1	2	1.0	209	2.0	231	2.3	5	
	Unknown	46	0.2	0	0.0	19	0.2	27	0.3	0	
	Female	212	1	4	2	137	1.3	71	0.7	19	
	Male	17,685	85.5	193	98	10,457	98.6	7,035	71.1	11	
Gender <sup>a</sup>	Other	16	0.1	0	0	6	0.1	10	0.1	0	0.404
	Unknown	2,777	13.4	0	0	1	0.0	2,776	28.1	0	
	Vaccinated	528	2.6	12	6.1	495	4.7	21	0.2	23	
Prior smallpox vaccination	Not vaccinated	2,974	14.4	94	47.7	2,758	26.0	122	1.2	32	0.334
vaccination	Unknown	17,188	83.1	91	46.2	7,348	69.3	9,749	98.6	5	
	PEPV	42	0.2	0	0	40	0.4	2	0	0	
·	PPV	1	0	0	0	1	0	0	0	0	
Smallpox vaccination	PEPV/PPV	4	0	0	0	2	0	2	0	0	0.461
for current event	Not vaccinated	3,017	14.6	101	51.3	2,798	26.4	118	1.2	33	
	Unknown	17,626	85.2	96	48.7	7,760	73.2	9,770	98.8	5	
	Positive	3,070	14.8	37	18.8	2,697	25.4	336	3.4	12	
HIV status	Negative	5,187	25.1	52	26.4	4,536	42.8	599	6.1	10	0.441
	Unknown	12,433	60.1	108	54.8	3,368	31.8	8,957	90.5	9	
	Yes	93	0.4	8	4.1	81	0.8	4	0	86	
STI	No	625	3	44	22.3	537	5.1	44	0.4	70	0.67
	Unknown	19,972	96.5	145	73.6	9,983	94.2	9,844	99.5	7	· ·
	MSM	8,777	42.4	84	42.6	6,677	63	2,016	20.4	10	
	Bisexual	93	0.4	4	2	80	0.8	9	0.1	43	Not
Sexual orientation	Heterosexual	276	1.3	9	4.6	242	2.3	25	0.3	33	calculated
	Unknown	11,544	55.8	100	50.7	3,602	34.0	7,842	79.2	13	
	Yes	64	0.3	0	0	56	0.5	8	0.1	0	
Health worker	No	3,645	17.6	80	40.6	3,334	31.4	231	2.3	22	0.64
	Unknown	16,981	82.1	117	59.4	7,211	68	9,653	97.6	7	
Rash	Not reported	657	3.2	4	2.0	424	4.6	229	2.0	6	
	Reported	12,415	60.0	187	94.9	8,367	90.1	3,861	34.4	15	0.085
	Unknown/no data on symptoms	7,618	36.8	6	3.0	494	5.3	7,118	63.5	1	
	Not reported	7,837	37.9	91	46.2	5,118	55.1	2,628	23.4	12	
Lymphadenopathy	Reported	5,235	25.3	100	50.8	3,673	39.6	1,462	13.0	19	0.005
,	Unknown/no data on symptoms	7,618	36.8	6	3.0	494	5.3	7,118	63.5	1	
	Not reported	4,596	22.2	91	46.2	2,917	31.4	1,588	14.2	20	
Systemic symptoms <sup>b</sup>	Reported	8,476	41.0	100	50.8	5,874	63.3	2,502	22.3	12	<0.001
e,sterme symptoms	Unknown/no data on symptoms	7,618	36.8	6	3.0	494	5.3	7,118	63.5	12	

MSM: men who have sex with men; PEPV: Post-exposure preventive vaccination; PPV: Primary preventive (pre-exposure) vaccination; STI: sexually transmitted infection.

<sup>a</sup> Gender collected in TESSy as female, male, other (e.g. transgender) or unknown.

<sup>b</sup> Fever, fatigue, muscle pain, chills and/or headache.

Based on case-based data reported in TESSy, hospitalisation ratios and p values were calculated for cases for whom hospitalisation status (i.e. not hospitalised, hospitalised for isolation purposes (n = 129 cases) or hospitalised for clinical management purposes (n = 197 cases)) was known. Cases whose hospitalisation status was reported as unknown or who were known to have been hospitalised, but purpose (isolation/clinical management) was unknown (n = 254) were not included in the analyses. 'Hospitalisation' is defined as hospitalisation for clinical care (n = 197 cases). Hospitalisation for known isolation (n = 129 cases) is included as 'Not hospitalised'. P values were calculated by Fisher's exact test. For each tabulation of hospitalisation (yes/no) by another variable, when one of the cells was equal to 0, 0.5 was added to all cells of the table in order to be able to conduct the statistical test.

All variables excluding vaccination are up to 23 August 2022. Smallpox vaccination variables combine data from 10 August 2022 and 23 August 2022 for completeness.

**TABLE 2** 

Exposure settings for monkeypox cases, 36 WHO European Region countries, 7 March-23 August 2022 (n = 20,690 cases)

Husehold      Mork      School/ nusery      Heatthcare        n      %      n      %      n      %        sees      20,690      100      233      100      48      n      %      n      %        sees      20,690      100      233      100      48      100      0<	Ľ												
Household      Work      Schooly nursery      Heathcare nursery        n      %      n      %      n      %      n      %        aises      20,690      100      233      1.00      48      1.00      0      0      0      0        aises      20,690      100      233      1.00      48      1.00      0 <th></th> <th>(n = 3,643 cases reporting at least one setting)</th> <th>orting at  </th> <th>least or</th> <th>ie settin</th> <th>g)</th> <th></th> <th></th> <th></th> <th></th> <th></th> <th></th> <th></th>		(n = 3,643 cases reporting at least one setting)	orting at	least or	ie settin	g)							
ases      0      %      1      %      1      %      0      %      0      %      1        ases      20,690      100      23      100      48      100      0      0      0      0      2,530        bup (verst)      41      0.2      3      13      0      0.00      0      0      0      0      3/5        for and the second structure      5,078      24,5      59      12,8      37,5      0      0      0      0      50      53      5        for and the second structure      8,231      39,8      99      4,27      18      37,5      0      0      0      0      5      5      5      5      10,4      0      0      10,0      5		Private party/ club with sexual activity	Large event with sexual activity		Large event w/o sexual activity		Bar/ restaurant w/o sexual activity		Other		Unknown	Missing	ing
ases      20,600      100      23      100      48      100      2,530        vup (versy)      41      0.2      3      1.3      00      0.0      0      0      2,530        41      0.2      3      1.3      0      0.0      0      0      0      375      0      0      0      0      337        5,078      24,5      59      25,4      18      375      0      0      0      0      0      50      53        8,231      39.8      99      4,27      18      375      0      0      0      0      0      0      50      53        4,42      211      4      1,7      1      2,1      0      0      0      0      0      35      5      5      5      5      10,4      0      0      2      5      5      5      5      5      5      5      5      5      5      5      5      5      5      5      5      5	u %	n %		%	n %		%		%		%		%
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41      0.2      3      1.3      0      0.0      0      0      0      3        5,078      24.5      59      25.4      18      37.5      0      0      0      0      653        8,231      39.8      99      42.7      18      37.5      0      0      0      0      0      633        4,970      24.0      53      22.8      6      12.5      0      0      0      0      0      585        4,970      24.0      53      22.8      6      12.5      0      0      0      0      0      0      585        4,970      24.0      14      1.7      1      2.1      1      2.1      1      2.1      2													
5,078      24,5      59      25.4      18      37.5      0      0      0      6      53        8,231      30.8      99      42.7      18      37.5      0      0      0      0      6      533        4,970      24,0      53      22.8      6      12.5      0      0      0      0      0      585        4,970      24,0      53      22.8      6      12.5      0      0      0      0      0      585        44      1,1      1      2,1      1      2,1      0      0      0      0      0      375        44      1,7      1      2,1      1      2,1      1      2,1 </td <td>0 0 0</td> <td>3 0.1</td> <td>0</td> <td>0.0</td> <td>1 0.</td> <td>2 1</td> <td>0.5</td> <td>4</td> <td>0.4</td> <td>e</td> <td>0.3</td> <td>30</td> <td>0.2</td>	0 0 0	3 0.1	0	0.0	1 0.	2 1	0.5	4	0.4	e	0.3	30	0.2
8.231      39.8      99      4.2.7      18      37.5      0      0      0      0      1.033        4.970      24.0      53      22.8      6      12.5      0      0      0      0      585        1.882      9.1      14      5.0      54      52.8      6      12.5      0      0      0      0      585        1.882      9.1      14      5.0      14      1.7      0      0      0      0      238        1.4      1.5      4      1.7      1      2.1      0      0      0      0      238        1.5      12      12      12      12      0	0 0	633 25.1	82 2	21.8 1	152 23.4	4 43	21.8	243	24.2	262	26.2	3,947	24.5
	0 0	1,033 41.0	184 4	48.8 2	290 44.7	.7 82	41.6	440	43.8	438	43.8	6,323	39.3
	0 0	585 23.2	82 2	21.8 1	154 23.7	.7 50	25.4	228	22.7	229	22.9	3,907	24.3
	0 0 0	228 9.0	26 0	6.9	48 7.4	4 18	9.1	72	7.2	59	5.9	1,521	9.4
b      17,685      98.7      214      91.8      48      100.0      0      0      0      2,512      9        1      17,685      98.7      214      91.8      7.7      0      0.00      0      0      0      18      7        1      16      0.1      1      0.4      0      0.0      0      0      0      18      7        1      16      0.1      1      0.4      0      0.0      0      0      0      18      7        1      93      0.1      1      0.4      0      0.0      0      0      0      0      0      0      10      0	0 0 0	39 1.5	3	0.8	4 0.6	6 3	1.5	18	1.8	10	1.0	374	2.3
	0 0 0	2,512 99.3	374 9	98.9 6	641 98	8.3 192	96.5	981	97.4	1,000	9.66	13,182	98.7
	0 0 0	18 0.7	4	1.1	11 1.7	7 7	3.5	24	2.4	m	0.3	161	1.2
orientation      8,777    75.7    172    86.0    32    86.5    0    0    0    0    2,325    5      al    93    0.8    12    6.0    1    2.7    0    0    0    0    2,325    5      sexual    23    0.8    12    6.0    1    2.7    0    0    0    2,325    5    5      sexual    276    2.4    14    7.0    3    8.1    0    0    0    2,325    5    5      worker    5    2.4    14    7.0    3    8.1    0    0    0    30    30    37    5	0 0 0	0 0.0	0	0.0	0.0 0.0	0 0	0.0	2	0.2	1	0.1	13	0.1
8,777      75.7      172      86.0      32      86.5      0      0      0      0      2,325      5        al      93      0.8      12      6.0      1      2.7      0      0      0      0      2,325      5        sexual      276      2.4      14      7.0      3      8.1      0      0      0      21      0      21      6        worker      2.4      14      7.0      3      8.1      0      0      0      30      21      6      21      9      21      9      21      9      21      9      21      9      21      9      21      2      20      20      0      21      20      21      20      21      20      21      20      21      20      21      21      20      20      20      21      20      21      21      21      21      21      21      21      21      21      21      21      21      21      21													
all      93      0.8      12      6.0      1      2.7      0      0      0      0      21      0        sexual      276      2.4      14      7.0      3      8.1      0      0      0      0      30      21      9        worker      276      2.4      14      7.0      3      8.1      0      0      0      30      30      3        worker      64      1.7      4      2.4      0      0.0      0      0      11      30      3      3      36      36      9      3	0 0 0	2,325 97.7	339 5	97.7 5	532 93.5	.5 138	88.5	868	93.0	698	70.6	4,936	67.5
sexual  276  2.4  14  7.0  3  8.1  0  0  0  30  30    worker	0 0 0	21 0.9	4	1.2	13 2.3	3 5	3.2	20	2.1	16	1.6	35	0.5
worker      64    1.7    4    2.4    0    0.0    0    0    0    11    11      3,645    98.3    162    97.6    46    100.0    0    0    0    865    9      kely mode of transmission <sup>c</sup> 359    5.3    42    21.4    6    16.2    0    0    0    82    1      6,385    93.9    153    78.1    30    81.1    0    0    0    1,341    9      11    0.2    0    0    1    2.7    0    1,341    9	0 0 0	30 1.3	4	1.2	23 4.0	0 13	8.3	35	3.8	44	4.4	147	2.0
64      1.7      4      2.4      0      0.0      0      0      0      11      11        3,645      98.3      162      97.6      46      100.0      0      0      0      865      9        kely mode      0      53.6      98.3      162      97.6      46      100.0      0      0      0      865      9        kely mode      0      162      0      0      0      0      0      865      9        359      5.3      42      21.4      6      16.2      0      0      0      82      134        359      93.9      153      78.1      30      81.1      0      0      0      1341      9        11      0.2      0      0.0      1      2.7      0													
3,645      98.3      162      97.6      46      100.0      0      0      0      865      9        kely mode of transmission      359      5.3      42      21.4      6      16.2      0      0      0      865      9        66,385      93.9      153      78.1      30      81.1      0      0      0      1341      9        11      0.2      0      0.0      1      2.7      0<	0 0 0	11 1.3	5	1.8	8 1.5	5 3	1.8	29	3.6	11	1.8	11	0.8
kely mode of transmission <sup>c</sup> 359    5.3    42    21.4    6    16.2    0    0    0    82      6,385    93.9    153    78.1    30    81.1    0    0    0    1,341      11    0.2    0    0.0    1    2.7    0    0    0    0	0 0 0	865 98.7	270 9	8.2	528 98.5	.5 168	98.2	787	96.4	601	98.2	1,285	99.2
359      5.3      42      21.4      6      16.2      0      0      0      0      82      82        6,385      93.9      153      78.1      30      81.1      0      0      0      0      1341        11      0.2      0      0.0      1      2.7      0      0      0      0      0      0													
6,385      93.9      153      78.1      30      81.1      0      0      0      0      1,341        11      0.2      0      0.0      1      2.7      0      0      0      0      0	0 0 0	82 5.8	6	2.0	54 10.1	.1 37	98.2	70	8.1	14	2.5	148	3.8
11      0.2      0      0.0      1      2.7      0<	0 0	1,341 94.1	292 9	97.7 4	475 88.	.8 131	75-7	791	91.2	547	97.2	3,698	95.3
	0 0 0	0.0	0	0.0	0.0	0	0.0	m	0.3	7	0.4	9	0.2
Other <sup>d</sup>   41 0.6 1 0.5 0 0.0 0 0 0 0 0 2 0	0 0 0	2 0.1	1	0.3	6 1.1	1 5	2.9	3	0.3	0	0.0	28	0.7
Sexual and PTP      1      0.0      0      0.0      0	0	0.0	0	0.0	0.0	0	0.0	0	0.0	0	0.0	1	0.0

<sup>a</sup> Possible exposure in the 21 days before symptom onset. Multiple exposures per case possible.

<sup>b</sup> Gender collected in TESSy as female, male, other (e.g., transgender) or unknown (not shown in table).

· No cases reported 'most likely mode of transmission' as zoonotic, occupational healthcare, occupational laboratory, vertical or transfusion.

<sup>d</sup> Many cases reporting 'other' route of transmission, also reported sexual, PTP or fomite transmission and exposure at a bar etc. (see text). Further details were not provided.

#### TABLE 3

Outcome by prior smallpox vaccination status among monkeypox cases, 36 WHO European Region countries, 7 March-23 August 2022 (n = 3,502 cases)

Veriebles		Vaccin	ated	Unvaccinated					
Variables			%		%	Crude OR	95% CI	Adjusted OR	95% CI
Total cases		528	15.1	2,974	84.9				
	18-30	49	5.7	817	94.3	Ref	Ref	Ref	Ref
	0-17	0	0	10	100	0.79	0.01-6.26	7.95	1.46-30.44
	31-40	94	6.8	1,298	93.2	1.20	0.85-1.73	0.97	0.61–1.57
Age group (years)	41-50	130	16.0	680	84.0	3.17	2.26-4.50	0.87	0.50-1.51
	51-60	189	58.9	132	41.1	23.62	16.56-34.24	0.3	0.08-0.86
	> 60	62	69.7	27	30.4	37.53	22.30-64.83	0.77	0.15-2.61
	Unknown	4	28.6	10	71.4	Not o	alculated	Not calculated	
	Male	516	15.0	2,927	85.0	Ref	Ref	Not calculated	
Gender <sup>a</sup>	Female	11	19.6	45	80.4	1.43	0.71-2.66		
	Other	1	33.3	2	66.7	3.40	0.31-25.62		
	Not hospitalised	495	15.2	2,758	84.8	Ref	Ref	Ref	Ref
Hospitalisation <sup>ь</sup>	Hospitalised	12	11.3	94	88.7	0.74	0.39-1.29	1.07	0.53-1.97
	Unknown	21	14.7	122	85.3	Not o	calculated	Not cal	culated
	No	253	15.0	1,437	85.0	Ref	Ref		
Health worker	Yes	2	4.9	39	95.1	0.36	0.36 0.07-1.07		culated
	Unknown	273	15.4	1,498	84.6	Not calculated			

CI: confidence interval; OR: odds ratio; Ref: reference.

<sup>a</sup> Gender collected in TESSy as female, male, other (e.g. transgender) or unknown (not shown in table).

<sup>b</sup> Hospitalisation is defined as hospitalisation for clinical care (n = 197). Hospitalisation for known isolation (n = 129) is included as not hospitalised for clinical care. Regressions were performed for cases for which there was complete data for the specific variables included in each model. Adjusted OR includes hospitalisation as a binary outcome and age (categorical) and vaccination (binary) as explanatory variables. Vaccinated include those vaccinated for smallpox prior to this outbreak.

years, sporadic cases and clusters of MPXV Clade II have occurred in other regions, largely linked to travel from endemic countries or imported animal to human transmission with limited onward human-to-human spread [8-16].

Transmission of MPXV is thought to occur primarily through close or direct physical contact with infected lesions, respiratory droplets or contaminated material [17]. Other transmission routes such as zoonotic or mother-to-child have been described [18]. Previously, typical clinical presentation was described as a prodromal phase, with fever, followed by a widespread, centrifugal, evolving maculopustular rash and lymphadenopathy [19]. People living with untreated HIV infection, pregnant women and young children have previously been identified to be at higher risk of severe MPX [20,21]. Epidemiological studies estimated that prior smallpox vaccination provides ca 85% crossprotection against MPXV and reduces the frequency and severity of symptoms [22,23]. However, routine vaccination was discontinued worldwide following the eradication of smallpox in 1980 and effectiveness of vaccination in the current outbreak remains to be assessed.

We describe an on-going multi-country outbreak of MPXV, mainly transmitted among MSM through close

physical contact, often during sexual activities. A large proportion of cases (94%) reported sexual transmission, often at gatherings and events which provided the opportunity for amplification through sexual networks. A smaller number of cases were also steadily reported among women and children. Nowcasting estimates suggest that reported cases have plateaued overall in Europe, however, some countries continue to see an increase. Such variation in projections by country may reflect potential differential implementation and impact of local intervention measures.

Clinical presentation in the current epidemic is atypical compared with previous outbreaks [24,25]. Symptoms involve an atypical rash-illness presentation, with a relatively low, but still notable proportion of patients hospitalised. Severe manifestations such as encephalitis have been reported in a small number of cases [26]. This clinical picture may change in the event of spread into populations with increased risk of severe disease, including those with untreated HIV or otherwise immunosuppressed. Further investigations are required to assess disease severity in immunocompromised individuals and other potential vulnerable groups for the current outbreak. We found no evidence that prior smallpox vaccination significantly protects against severe disease and hospitalisation, which raises questions regarding potential waning protection

following vaccination over 4 decades ago. As smallpox vaccines are currently rolled out to at-risk individuals, it is essential that studies are undertaken to understand vaccine effectiveness.

This study has some limitations. The analyses are based on surveillance data submitted to TESSy, which are dependent on availability of data at national level and vary in completeness. Indeed, for a number of variables, including vaccination, the level of missing data makes interpretation of analyses challenging. In addition, any clinical data reported in TESSy is of limited scope and will not reflect the full course of disease. Finally, while nowcasting is a valuable tool to account for delays in reporting, interpretation should consider that missing data and misclassification of symptom onset date and varying reporting delays over time can contribute to a considerable uncertainty around these estimates.

#### Conclusions

To interrupt transmission of MPXV, identification and testing, management of cases and contacts, targeted risk communication and strong community engagement with affected groups, implementation of targeted public health measures, combined with PPV/PEPV are fundamental [27-30]. However, the transmission patterns of the virus, coupled with the difficulty of tracing multiple often anonymous sexual contacts, likely under-ascertainment of cases, challenges to access and vaccinate priority groups and stigma complicate the public health response. An integrated response with strong collaboration among at-risk groups, communities, public health authorities, and international health organisations is required to overcome these challenges.

#### Ethical statement

Ethical approval was not needed for this study, which was based on surveillance data only.

#### Disclaimer

The authors affiliated with the World Health Organization (WHO) are alone responsible for the views expressed in this publication and they do not necessarily represent the decisions or policies of the WHO. The co-author is a fellow of the ECDC Fellowship Programme, supported financially by the European Centre for Disease Prevention and Control (ECDC). The views and opinions expressed herein do not state or reflect those of ECDC. ECDC is not responsible for the data and information collation and analysis and cannot be held liable for conclusions or opinions drawn.

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Anna Marie Theut (Statens Serum Institut, Copenhagen,

#### **Conflict of interest**

None declared.

#### Authors' contributions

AMV, OC, SC, LdSA, NF, JP, GS, CMG, RP and JMH drafted the manuscript. GA, MA, SB, PB, AC, EC, OC, AD, CD, ID, KK, MF, FF, RF, JF, CF, MGC, KG, MPG, BRGH, JH, EH, DI, MI, KJ, DGJ, TBJ, AK, AK, JK, JVM, AM, KM, ZM, ZM, JM, AN, HO, IPN, MKR, MST, CS, DS, AS, KS, AT, MT, MT, VU, CvE, JV, AV, RV and KZ conducted MPX surveillance and data collections in their respective countries. All authors read, revised and approved the final manuscript.

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