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Scientific letter

Monkeypox in children and adult women in Europe: Results from a flash VACCELERATE pilot survey

Viruela del Mono en Población Pediátrica y Mujeres Adultas en Europa: Resultados de una Encuesta Piloto de VACCELERATE

As of August 5th, 2022, the World Health Organization (WHO) confirmed 26,017 cases of human monkeypox in the ongoing 2022 multi-country outbreak. Most persons were male and the median age was 37 years.[1] A significant number of cases is reported among men who have sex with men (MSM). It is assumed that close contact during sexual intercourse may be the driving force behind this recent human-to-human transmission in high income countries.[2]

First monkeypox cases in humans were reported in the 1970s from the endemic regions of Western and Central Africa. Occasionally, these have been self-limited to zoonotic infections from rodents and primates to humans. Contrary to the current outbreak, a disproportionate number of cases have been described among children.[3] Between 1980 and 1984, 111 out of 214 patients (51.9%) with primary infections due to the Central African clade, from the former Republic of Zaire, currently Democratic Republic of Congo, were under the age of 4, and 87 (40.7%) between the age of 5 and 14.[4] Unvaccinated young males were probably at greater risk because of their exposure to mammals during hunting and playing activities.[5] Secondary human-to-human transmission was predominately observed in children. More women were affected by secondary infections, suggesting child-to-mother transmission.[3]

As monkeypox infections increased in the 2000s, there seems to be a trend towards young adults in their twenties being affected.[6] This tendency has been explained by several factors. It is important to note that the endemic regions of Africa have a much younger population than most of the world.[7] However, the main reason for this change in age might be related to the presumably low vaccination coverage with the smallpox vaccine, which could provide some cross-protection against monkeypox.[6] Since the smallpox virus has been declared eradicated in 1980, vaccination ceased to <30% of the global population.[8] While most known outbreaks in the past were ascribed to the Central African clade, the 2022 multi-country outbreak is caused by the less severe Western African clade. This clade has only recently become an unexpected issue of concern to health authorities in West Africa, suggesting changes in monkeypox virus epidemic dynamics.[6]

While the focus has been on MSM, little has been written about other populations at risk. With this flash survey we intended to gather valuable information in order to appropriately design future specific studies on vulnerable populations such as children and women and the current epidemiological situation in Europe. Especially considering that children are experiencing more complications and a higher mortality. In pregnant women vertical transmission has moreover been associated with stillbirth and congenital infection.[9]

Between July 13th and August 3rd, 2022, 88 institutions from 27 European countries participated in our flash online survey regarding the prevalence of monkeypox in children and adult women in Europe (Fig. 1).

In this online survey under the umbrella of the VACCELERATE Consortium (https://www.clinicalsurveys.net/uc/VACC_MPX_women_and_children/),[10] participating institutions were asked to provide their numbers on persons evaluated for monkeypox and for confirmed cases locally, as well as the number of confirmed cases nationally. The largest numbers of evaluated children were reported from Belgium ($n = 47$) and the United Kingdom ($n = 20$). However, Spain (1.00) and Germany (0.33) were the countries with the highest ratios of confirmed cases. Spain ($n = 226$) and Belgium ($n = 60$) had the largest number of women evaluated for monkeypox. Among evaluated women the highest likelihood of infection was reported from Spain (0.08) and Portugal (0.06).

Additionally, all institutions were asked about their current treatment options and plans for treatment of monkeypox infections in children (classified as infants [0–1 year], toddlers [1–3 years], pre-schoolers [3–5 years], middle childhood [6–11 years], young teens [12–14 years], and teenagers [15–17 years]). Of 88 institutions participating in this survey, five (5.7%) reported confirmed cases. One institution from the United Kingdom reported consideration of off-labelled use of Imvanex® for post-exposure prophylaxis at any age and tecovirimat for treatment in infants. Two institutions from Spain, and one institution from Germany did not report having provided any specific treatment and one from Spain did not answer to this question.

With this flash survey, we would like to raise the need to raise awareness in populations such as children and adult women, as they can also develop monkeypox infection.

Authors' contributions

JHG, OAC, and JSG contributed to study design and conceived the study idea.

JSG collected and validated the data, did the statistical plan and analysis.

JHG and JSG drafted the first version of the manuscript.

All authors contributed to data interpretation, manuscript writing and review of the manuscript.

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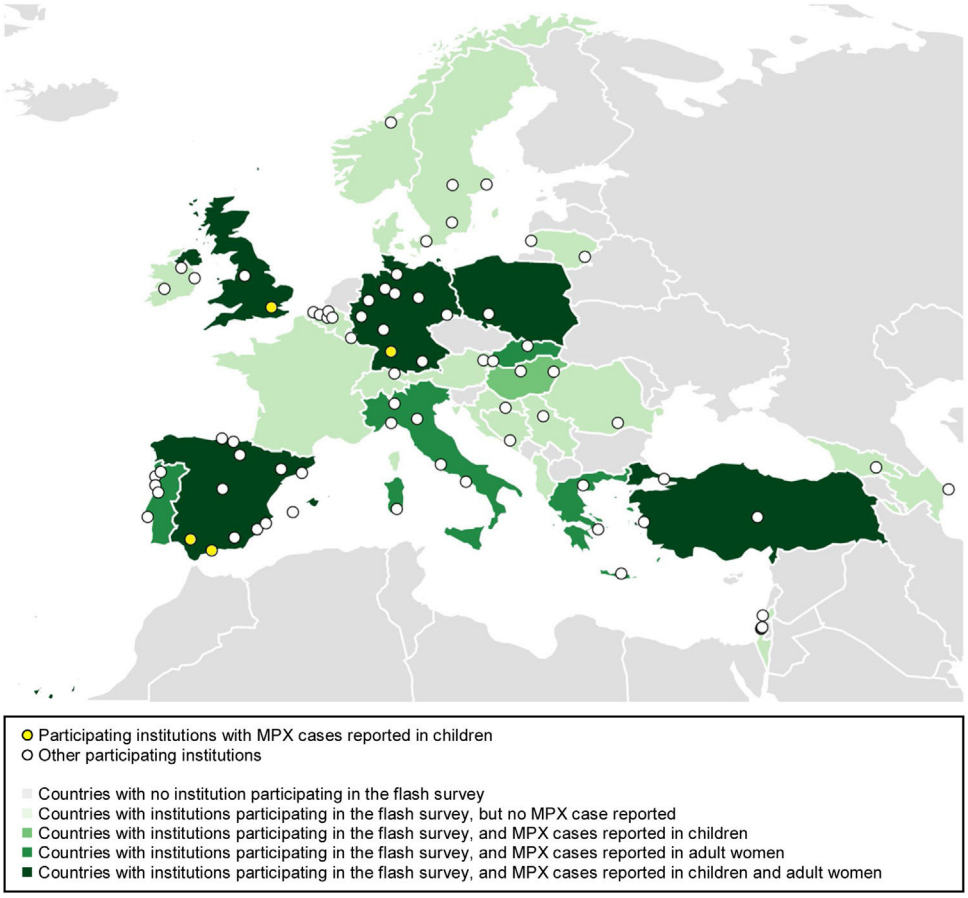

Fig. 1. Distribution of participating institutions. Origin countries of participating institutions: Spain ($n = 18$ [20.5%]), Germany ($n = 11$ [12.5%]), Portugal ($n = 7$ [8.0%]), Italy ($n = 6$ [6.8%]), Belgium, Greece, and Turkey ($n = 5$ [5.7%], each), Israel and Sweden ($n = 4$ [4.5%], each), Ireland ($n = 3$ [3.4%], Hungary, Lithuania, and United Kingdom ($n = 2$ [2.3%], each), and Albania, Austria, Azerbaijan, Bosnia and Herzegovina, Croatia, Denmark, Georgia, Luxembourg, Norway, Poland, Romania, Serbia, Slovakia, and Switzerland (1 [1.1%], each). MPX, monkeypox.

Conflict of interests

JHG reports no conflicts of interest.

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Molecular characterization of *Staphylococcus aureus* causing menstrual toxic shock syndrome in a young woman

Caracterización molecular de Staphylococccus aureus, *agente causal del síndrome del shock tóxico menstrual en una mujer joven*

Toxic shock syndrome (TSS) is a rare life-threatening disease first described by Todd and Fishaut in 1978. The most characteristic symptoms are fever, rash, hypotension, desquamation and the involvement of multiple organ systems.[1] Menstrual TSS (mTSS) is defined when it appears from the beginning of the menstruation and up to four days after.[2] mTSS incidence has been reported to be 0.69 in 100,000 menstruating women per year and has been associated with high morbidity and mortality rate in previously healthy women.[3]

mTSS is caused by superantigen-producing *Staphylococcus aureus* (SA) or group A *Streptococcus,* and has been associated with the use of different vaginal devices as tampons or menstrual cups.[4] SA superantigen, named toxic shock syndrome toxin-1 (TSST-1), is encoded by *tst* gene and is responsible for mTSS by its ability to trigger excessive and non-conventional T-cell activation with consequent downstream activation of other cell types, and cytokine/chemokine release.[5]

We report a case of a 15-year-old menstruating woman who was hospitalized in the Intensive Care Unit (ICU) with suspicion of septic shock in the context of purulent vaginal discharge. The presented symptoms were malaise, fever (38.9 °C), sore throat, diarrhoea, rash and painful genital ulcers of 3 days of evolution. Physical examination was remarkable for a low blood pressure (80/50 mmHg), diffuse erythematous macular rash and conjunctival hyperaemia. Laboratory assessments on admission revealed elevated inflammatory markers (value obtained – reference range) (CRP 218 mg/L – 0.2–5 mg/L; PCT 26.65 ng/mL – <0.05 ng/mL), acute renal injury (creatinine 3 mg/dL – 0.51–0.95 mg/dL), anaemia (haemoglobin 10.5 g/dL), thrombocytopenia (101×10^9 platelets/L) and associated coagulopathy (D-dimers 6634 ng/mL – 0–243 ng/mL). Upon ICU admission, several samples were sent to the laboratory for bacteriological study and SA was isolated from vaginal, nasal, rectal and axillary swabs, pointing out the mTSS as the most probable diagnosis. Blood cultures remained negative. Antibiotic susceptibility testing was performed with Panel Type 33 of MicroScan WalkAway using the breakpoints recommended by The European Committee on Antimicrobial Susceptibility Testing (http://www.eucast.org).

The four SA strains showed the same resistance phenotype (penicillin, erythromycin and clindamycin inducible (MLSBi)); they were sent to the University of La Rioja for detection of (1) virulence genes: *tst* (encoding TSST-1 toxin), *pvl* (encoding Panton-Valentine-Leucocidin) and *sea*, *seb* and *sec* (encoding enterotoxins A, B and C); (2) antimicrobial resistance genes (*blaZ* and *ermA/ermB/ermC/ermT*); (3) molecular typing (*spa*-typing and multi-locus-sequence-typing); (4) immune evasion cluster (IEC) system, present in most human SA isolates (the IEC system includes seven different types: from A to E).[6]

The four isolates were typed as MSSA-CC30-t012 and IEC-type A, they carried the *tst* gene (verified by PCR/sequencing) but not *pvl* and they carried the *blaZ* gene (Table 1); they also carried the *sea* gene but not *seb* or *sec* genes. The prevalence of CC30 SA has been considerably reported in several European countries[7,8]; and a study performed in the UK revealed a strong association of the *tst*-positive CC30 SA lineage with mTSS and TSS cases.[9]

However, mTSS primarily remains a clinical diagnosis, and indeed, the isolation of SA *tst*$^+$ is not required for diagnosis of the disease.[5] Moreover, in Spain and other countries in Europe, TSS is not a notifiable illness, so the clinical, microbiological, and toxigenic features of TSS remain poorly described.

The patient was empirically treated with cefotaxime and metronidazole. Metronidazole was discontinued and clindamycin was added when SA was reported. After antibiotic susceptibility testing, treatment changed from cefotaxime to cloxacillin and, since the patient was presenting a favourable evolution, clindamycin was maintained. The patient was discharged from ICU setting 2 days after admission, and sent home on the 8th day of hospitalization.

Table 1
Characterization of the four *Staphylococcus aureus* isolates recovered from the patient with menstrual toxic shock syndrome.

Sample	Molecular typing		Antimicrobial resistance		Virulence genes	IEC-type
	spa-type	CC	Phenotype[a]	Genotype		
Vaginal	t012	CC30	PEN, ERY, CLI[b]	*blaZ*, *erm*(A)	*tst*, ***sea***	A
Nasal	t012	CC30	PEN, ERY, CLI[a]	*blaZ*, *erm*(A)	*tst*, ***sea***	A
Rectal	t012	CC30	PEN, ERY, CLI[a]	*blaZ*, *erm*(A)	*tst*, ***sea***	A
Axillary	t012	CC30	PEN, ERY, CLI[a]	*blaZ*, *erm*(A)	*tst*, ***sea***	A

[a] PEN: penicillin; ERY: erythromycin; CLI: clindamycin.
[b] Inducible resistance.