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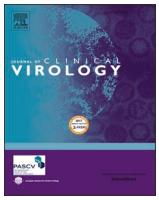

Review article

Detection of yellow fever virus genome in urine following natural infection or vaccination: review of current knowledge 1985–2023

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ABSTRACT

Background: Yellow fever virus (YFV) is endemic in the (sub)tropical regions of Africa and South America and is prone to cause epidemics. Molecular testing of YFV by reverse transcription-polymerase chain reaction (RT-PCR) was recently adopted by WHO using blood. Urine is a non-invasive diagnostic specimen which has been proven to be useful in diagnosing several flavivirus infections. Until now, systematic data on the usefulness of urine in YFV molecular diagnostics was lacking.

Methods: We have carried out an extensive literature search using key words "yellow fever AND urine" in PubMed/Medline, Embase and Web of Science.

Results: The search resulted initially in 113 publications. All titles and abstracts were screened and 15 were analyzed in detail. After natural infection (10 articles), the detection ratio of YFV in blood with RT-PCR was 61 % (105/171 samples) vs. 59 % (139/234) in urine from patients with mild/severe infections. YFV could be first detected at average 4.3 days in blood vs. 6.1 days in urine and last detected till 17.2 vs. 31.1 days respectively (significant difference $p < 0.05$). Viral load over time in blood was not statistically different from urine. Virus could be isolated from blood, urine and semen. Following vaccination, virus was detected longer in patients with vaccine adverse events (VAE) compared to healthy vaccinees (average 34 vs. 25 days, not significant $p > 0.05$).

Conclusion: YFV can be detected in urine later but longer. Thus, we see added value for YF molecular diagnostics and sequencing and recommend it besides blood as a standard specimen, especially for late samples post onset.

1. Introduction

Yellow fever virus (YF) is a mosquito borne arbovirus with a positive strand RNA genome, and is a member of the *Orthoflavivirus* genus [1]. The virus is thought to have originated in Central Africa 700–1200 years ago [2]. It is endemic in the tropical and subtropical regions of Africa and South America and periodically causes local and regional epidemics [2]. Large outbreaks were reported in 2016, when YFV caused outbreaks in Angola, Democratic Republic of the Congo (DRC) [3] and Brazil [4]. The virus has three types of transmission cycles: forest or sylvatic, intermediate and urban. In the sylvatic cycle, non-human primates (NHP) are bitten by infected, wild *Aedes* mosquitoes (in Africa) or *Haemagogus* mosquitoes and other species (in South America) that transmit the virus to other NHP and occasionally to humans travelling or working in sylvatic regions; in the intermediate cycle (in Africa only) semi-domestic mosquitoes infect both NHP and people living or working in forest border areas; in the urban cycle, infected people introduce the virus into heavily populated areas with high domestic mosquito density where people have little immunity and human-vector-human transmission occurs [2,5]. Occasionally, infected travelers import the virus into countries where YFV is not present however, further transmission requires the presence of a competent mosquito vector. Both New and Old World NHP are susceptible to YFV infection however, at different levels. In Africa, the majority of NHP have asymptomatic or mild, although viremic, YFV infections [6]. In South America, NHP epizootics and die-offs are often used as warning signals in YFV surveillance [7].

In 1937 an effective vaccine was developed based on the Asibi strain of YFV [8,9] and vaccination is still the most effective preventive

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measure against YFV infection. A single dose of the live-attenuated YF virus vaccine evokes lifelong protective immunity in 80 %–100 % of recipients within 10 days and in 99 % within 30 days [10]. Vaccine failures are extremely rare (18/>540 million doses administered) [10], vaccine adverse events (VAE) and vaccine-associated disease can occur but rarely (4.4–4.7/ 100,000 vaccinated) [11-17].

In 2023, an updated YFV laboratory algorithm became available to advise on diagnostics both during outbreak and for surveillance purposes [18]. Laboratory diagnosis used to rely on the detection of YF specific serum IgM antibodies using ELISA. However, IgM is often not sufficient to confirm infection as the response can be misinterpreted due to vaccine elicited IgM response, as well as cross reactivity with antibodies induced by infections with other locally circulating flaviviruses. Quantitative reverse transcription polymerase chain reaction (RT-qPCR) based molecular methods are now used as a baseline and confirmatory test of acute infection and have also the benefit to distinguish between vaccine and wild type YFV strains [18]. Blood (serum and EDTA-blood) is the most commonly used specimen for molecular testing, as well as post-mortem biopsies. Urine is a non-invasive, easily accessible diagnostic specimen also available in large quantities which has been proven to be useful in diagnosing several other flavivirus infections i.e. Zika virus, dengue virus, West Nile virus, because of the longer detectability compared to blood [19-22] (Review in preparation Pezzi et al.,). Until now, clear, systematic data on the usefulness of urine in YFV diagnostics was lacking.

In this review we have collated and analyzed the available literature about detection of YFV in urine by RT-qPCR both in naturally infected and vaccinated individuals in order to explore the diagnostic usefulness of this specimen and discuss the benefits, pitfalls and the knowledge gaps.

2. Methods

2.1. Literature search

The used search term was “yellow fever and urine”. The literature search was performed on 11–05–2023 and all records published until that date were considered, with no language or geographical restrictions. We have searched PubMed/Medline (1946-present), Embase (1971-present) and Web of Science Core Collection (1975-present). The exact search terms were the following: Medline, (Yellow Fever / OR Yellow Fever Vaccine / OR Yellow fever virus / OR (yellow-fever OR (yf ADJ3 (virus OR infect*))).ab,ti,kw.) AND (Urine / OR Urinalysis / OR Yellow Fever /ur OR Yellow Fever Vaccine /ur OR (urine* OR urinalys* OR Antigenuri*).ab,ti,kw.); Embase, (’yellow fever’/de OR ’yellow fever vaccine’/de OR ’yellow fever virus’/exp OR (yellow-fever OR (yf NEAR/3 (virus OR infect*))):Ab,ti,kw) AND (urine/exp OR ’urine sampling’/de OR urinalysis/exp OR (urine* OR urinalys* OR Antigenuri*):ab,ti,kw); Web of science, TS=(((yellow-fever OR (yf NEAR/2 (virus OR infect*)))) AND ((urine* OR urinalys* OR Antigenuri*))).

2.2. Inclusion, exclusion criteria and process

The search resulted initially in 184 hits which was reduced to 113 after de-duplication. All of these articles were screened by reading the titles and abstracts. During data extraction one more article was identified and like this in total 15 articles were included for full analysis. Reasons for exclusions during screening were: duplicate entries ($n = 2$), no abstract was available ($n = 3$), outdated records regarding the use of molecular testing (from before 1985) ($n = 13$), not related to YF or the topic ($n = 74$). Reasons for exclusion during eligibility checks were: reviews either already including the identified articles ($n = 2$) or broad reviews with other focus ($n = 2$), one record was focusing on kidney injury without any detail on YFV detection in urine, two records had no full text available. All articles, YF case reports, YF vaccination adverse event reports or any study detailing YF patients or vaccinees presenting data on the use of RT-qPCR testing in urine and blood (i.e. serum, plasma, whole blood, EDTA-blood, specified in brackets next to where data is discussed) were included. Languages other than English were also considered. Articles describing the use of urine for the diagnosis of other flaviviruses were excluded.

2.3. Analysis

All relevant data like country, amount and type of patients, all clinical information including severity, diagnostic methods, amount and type of samples and viral load over time and much more were manually extracted from the selected manuscripts and recorded in Microsoft Excel (Microsoft Corporation. Microsoft Excel. 2016. Available from: https://office.microsoft.com/excel) (Supplementary Figure S1). If sufficient details were given, data was organized and compared, and means were calculated. In Excel, two-sample *t*-test assuming unequal variances was used to compare various datasets regarding detection times post symptom onset, length of detection amongst vaccinated individuals with or without VAE and to compare detection ratio and viral load or PCR Ct values in blood to urine over time. For simplicity, plasma, serum, whole blood, EDTA-blood were collectively referred to as blood however, specified.

3. Results

3.1. Characteristics of included studies

Of the 15 articles included in the final selection, 10 described naturally infected individual cases (7 articles) or patient cohorts (3 articles) (publication years 2017–2022). Five articles described detection of virus in urine post vaccination both in healthy vaccinees and patients with VAE (publication years 2011–2020). Articles contained various level of information regarding days of virus detection post onset or vaccination, in blood and/or urine and viral load or PCR Ct values at a given time in the different specimens. All available data was collated and if possible, analyzed in depth.

3.2. RT-qPCR detection of yellow fever virus in urine in naturally infected patients

In total ten articles were identified; almost half of the studies originated from Brazil ($n = 4/10$), the remaining six articles described import cases to China ($n = 4$) from Angola, and to the Netherlands ($n = 2$), one from Brazil and another from Suriname (Table 1). The articles had slightly different focus, but they all used urine besides other specimen (blood, saliva and semen) to detect YFV by RT-qPCR. The clinical presentation varied from mild to severe and kidney injury was also reported (30 %, 63/212 patients). Virus was detected by RT-qPCR in blood (10/10 articles) (serum $n = 6$, unspecified blood $n = 2$, plasma $n = 1$, whole blood $n = 1$ and EDTA-blood $n = 1$), in one study in saliva and in two studies in semen. Virus was successfully isolated from serum (reported in $n = 1$ article) and urine ($n = 3$) at various time points. All studies, where attempted, used the RNA isolated from urine successfully for sequencing and genotyping. To investigate the molecular diagnostic utility of urine vs. blood, details about the amount of samples per patients, and detection at various days post symptom onset were compared (Table 2). Overall, YFV could be detected in blood in 61 % of all samples tested (105/171 samples) (on average from 4.3 to 17.2 days); in urine, successful detection was described in 59 % of samples (139/234) (on average from 6.1 to 31.1 days). Thus, virus could be detected in blood significantly earlier ($p = 0.04$) but longer in urine ($p = 0.04$). Seven studies reported RT-qPCR Ct values where more data was available for urine than for blood. RT-qPCR Ct values increased over time for both, and the mean Ct value was statistically different for whole blood vs. urine only (mean Ct serum 28 .1 vs. whole blood 31.8 vs. EDTA-blood 31.2 vs. urine 29.2, (Fig. 1). In paired blood and urine samples, during

Table 1
Overview of included articles where YFV was detected by various molecular methods in urine from naturally infected patients.

Reference	Year	Country	Patient type	Number of patients (number of samples)	Disease severity	Diagnostic method used	Which PCR used	Compared with other specimen	YFV lineage
Reusken et al.,	2017	Netherlands (import)	naturally infected	1 patient (9)	acute, severe	RT-qPCR	Domingo et al.,2012	serum	From Suriname, not specified
Cui et al.,	2017	China (import)	naturally infected	4 patients (7)	acute, severe	NGS and Sanger sequencing	not stated	serum, saliva	Angola 71
Song et al.,	2018	China (import)	naturally infected	10 patients (not stated >10)	acute, mild and severe	RT-qPCR and sequencing, ELISA	not stated	blood (not specified)	From Angola, not specified
Li et al.,	2019	China (import)	naturally infected	5 patients (18)	acute, mild and severe	RT-qPCR, NGS, virus culture	Domingo et al., 2018	serum	From Angola, not specified
Chen et al.,	2018	China (import)	naturally infected	12 patients (21) but partially overlapping dataset with Song and Li et al.,	acute, mild and severe	RT-qPCR, NGS	not stated but assumed Domingo et al., 2018	blood (not specified)	From Angola, not specified
Casadio et al.,	2019	Brazil	naturally infected	62 patients (65 + follow up, amount not specified)	acute, severe	RT-qPCR and Sanger sequencing	Domingo et al., 2018	serum	South American I (clade E1)
Barbosa et al.,	2018	Brazil	naturally infected	1 patient (5)	acute, severe	RT-qPCR, NGS, virus culture, IgM ELISA	Diallo et al., 2014	serum, semen	South America I
Moreira Salles et al.,	2022	Brazil	naturally infected	56 patients (56)	acute, severe	RT-qPCR and NGS	Domingo et al., 2018	plasma	South American I (clades E1 and 2)
Phan et al.,	2020	Netherlands (import)	naturally infected	1 patient (24)	acute, mild	RT-qPCR, NGS, virus culture, IgM IF	Domingo et al., 2012	whole blood, EDTA, semen	South America I
De Rezede et al.,	2022	Brazil	naturally infected	60 patients (68)	acute, mild to severe	RT-qPCR, Sanger sequencing	Domingo et al., 2012	serum	South America I

Table 2
Details of patients(cohorts), number of samples tested and detection of YFV RNA over time with RT- qPCR in urine and blood during natural infections.

Reference	Size of cohort	Amount of patients followed up till negative PCR (n/n)	Number of samples tested	YFV detected in blood (n/n)	%	YFV detected in urine (n/n)	%	Earliest DpO YFV detected in blood	Latest DpO YFV detected in blood	Earliest DpO YFV detected in urine	Latest DpO YFV detected in urine
Reusken et al.,	1	1/1	9	3/3	100	4/6	67	6	20	9	24
Cui et al., &	4	0/4	7	1/4	25	3/3	100	3	3	7	13^
Song et al., &	10	10/10	10#	not specified, assumed (10/10)	assumed 100	10/10	100	not specified	not specified	6	31
Li et al.,&	5	4/5	17	8/12	67	16/17	94	4	10	6	32
Chen et al.,&	9	9/9	10	1/10	10	7/10	70	6	6	6	20
Casadio et al.,	62	7/62	62	59/62	95	62/62	100	<5 days	28	not specified	47
Barbosa et al.,	1	1/1	5	0/2	0	2/2	100	not detected	not detected	10	21*
Phan et al.,	1	1/1	24	13/14	93	8/8	100	5	30 (in EDTA), 44 (in WB)	5	44*
De Rezede et al.,	60	60/60	68	2/8	25	15/60	25	3	4	3	69
Moreira Salles et al.,	56	0/56	56	18/56	32	22/56	39	2, early time points, mean 5.6 days (genotyping study)	10	3, early time points, mean 5.6 days (genotyping study)	10
Total/ average	209	93/149 (62 %)	258	105/171	61	139/234	59	mean 4.3	mean 17.2	mean 6.1	mean 31.1

(i) DpO: days post onset; EDTA: EDTA-blood; WB: whole blood (ii) & partially overlapping datasets # amount of samples not stated only the maximum number days of detection; *semen also positive; ^1/3 patient also positive in saliva.

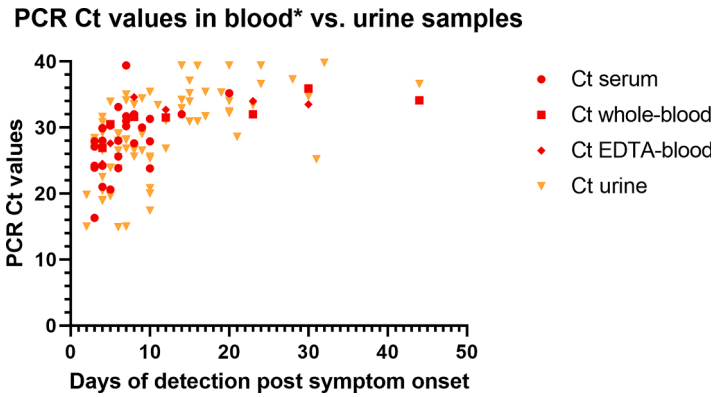

Fig. 1. Viral load (PCR Ct values) in blood versus urine over time.

natural infections, in 21 sample sets were urine positive and blood negative and only in one early sample set was urine negative and blood positive. Amongst vaccinees more data is available for urine testing only, nevertheless in 13 sample sets were urine positive and blood negative and in zero set was the opposite observed (Fig. 2). In these sample sets, in all cases (both natural infections and vaccination studies) virus was detected longer in urine. YFV specific IgM was not tested neither systematically nor longitudinally in these studies however, in five articles this was measured at different time points and both serum IgM and PCR was positive in urine, but this was not necessarily the case for blood (3/5 positive for both).

3.3. RT-qPCR detection of yellow fever virus in vaccinated individuals

We identified and analyzed five articles which described the detection of YFV RNA by RT-qPCR in urine post-vaccination (Table 3). Two of these were cohort studies; one study included both healthy vaccinees and patients with VAE from Liberia/Cameroon, the other included healthy vaccinees only from Spain. The other three articles were case studies of patients with VAE from Western Europe (two from Germany and one from France). The vaccine brand was specified in three articles (Stamaril, Sanofi Pasteur, France), whereas the other two studies only mentioned the use of 17D vaccine. YFV detection in urine was compared to blood (plasma and serum) in 3/5 articles, and in tracheal secretions in one article. YFV RNA was detected in a small proportion of the healthy vaccines (10.3 %, 6/58 from two pooled cohort studies), this proportion was higher for patients with VAE (52 %, 11/21). In three studies the viral load was stated; the viral load in urine was higher than in blood but differences were not significant (average urine 4.5 × 10^5 copies/ml (range 3 × 10^1 - 1.3 × 10^6) vs. blood 5.7 × 10^4 copies/ml (range 2 × 10^4 - 1 × 10^5)) and the day of sampling was not always the same. Based on data pooled from all five articles, virus was detected longer in patients with VAE compared to healthy vaccines (on average 33.6 days vs. 25) (Fig. 3), but the difference was not significant ($p > 0.05$). Shedding patterns seemed to be different between healthy vaccines and patients with VAE (short vs. long and intermitted) but this observation was based only on two studies.

4. Discussion

Molecular diagnostics enables the detection of YFV in a very sensitive and specific manner. In several studies, urine was successfully used to detect YFV in both naturally infected individuals and in vaccine recipients with or without VAE, with an extended window of detection compared to blood. This specimen therefore has benefits for patients presenting late after symptom onset and also as a non-invasive specimen. Furthermore, urine also has benefits for diagnostics as it is available in large quantities and does not require separation centrifugations unlike blood. Blood also has the risk of hemolysis, which could deem the sample unusable. Whether the presence of (hemolysed) blood

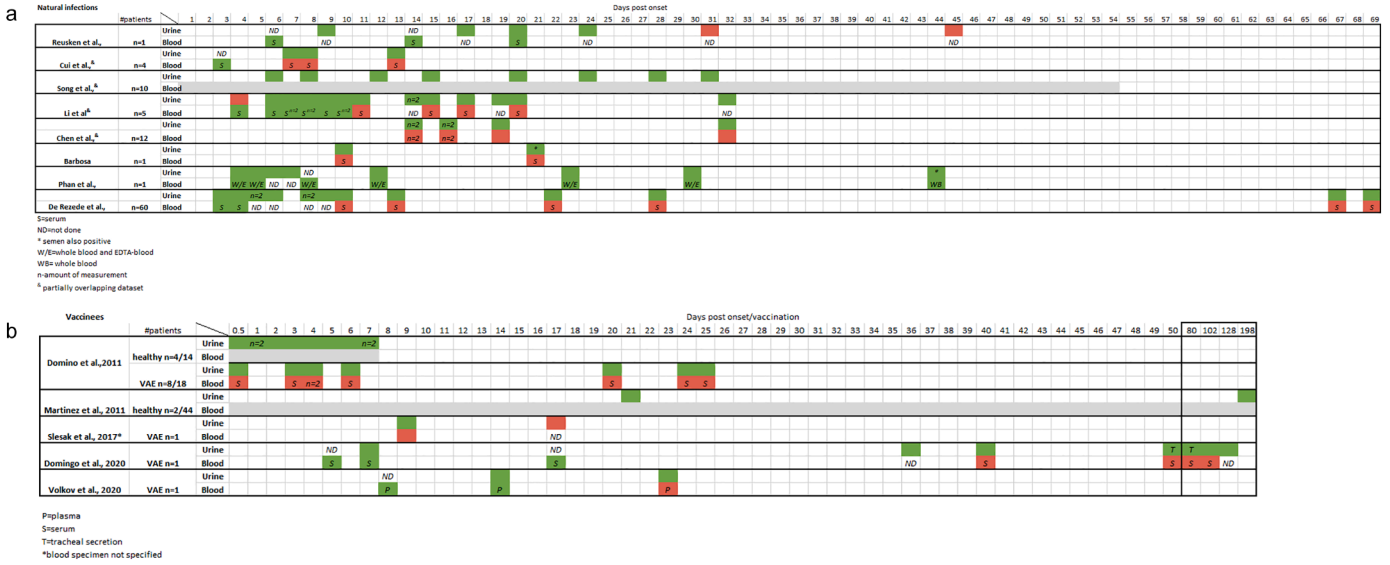

Fig. 2. Detection pattern of YFV genome in paired urine and blood samples. a, naturally infected individuals; b, vaccinated individuals.

Table 3
Detection of YFV with PCR in vaccinated individuals, both healthy or with vaccine adverse event (VAE).

Reference	Year	Country	Patient type	Vaccine type	YF RNA detection in urine, days post vaccination	Number of patients (number of samples)	Disease severity	Proportion of patients (urine samples) RNA detected	Diagnostic method used	Which PCR used	Compared with other specimen	Viral load (copies/ml)
Domingo et al.,	2011	Liberia and Cameroon	vaccinated	17D (not specified)	between 0 and 28 days	32 vaccinees (129)	14 healthy vaccinees, 18 with suspect VAE	4/14 and 8/18 (18/129)	RT-qPCR	Bae et al.,	none, urine only	urine: average viral load 8.8×10^2; range 30/70 to 10^4
Martinez et al.,	2011	Spain	vaccinated	17D (not specified)	21 and 198	44 vaccinees (44)	healthy vaccinees	2/44 (2/44)	RT-qPCR	not stated specifically, NS5 targeted	none, urine only	not stated
Slesak et al.,	2017	Germany	vaccinated	Stamaril	9 days	1 patient (multiple)	VAE, severe	1/1 (1/2)	IF IgG/IgM, RT-qPCR, $PRNT_{90}$	Domingo et al., 2012	blood (not specified)	not stated
Domingo et al.,	2020	Germany	vaccinated	Stamaril	from 7 to 100 days	1 patient (multiple)	VAE, severe	1/1 (7/13)	IF IgG/IgM, RT-qPCR, $PRNT_{90}$,	not stated but Domingo et al., 2012 assumed	serum, plasma, tracheal secretion	serum: viral load 8 days post onset 1×10^5; urine: viral load 7 days post onset1.3×10^6
Volkov et al.,	2020	France	vaccinated	Stamaril	14 and 23 days	1 patient (multiple)	VAE, severe	1/1 (2/2)	IgG, IgM, RT-qPCR	Escadalfa et al., 2014	plasma	plasma: 14 days post onset 2×10^4; urine 14 post onset 5×10^5
Total/ average	/	/	/	/	median 22, range 0–198	69	/	healthy 6/58 and VAE 11/21	/	/	/	urine: 4.5×10^5 (range 3×10^1–1.3×10^6), blood: 5.7×10^4 (range 2×10^4–1×10^5)

in urine during the hemorrhagic course of illness would be inhibitory for PCR, is not known [23-25]. Besides the clear benefits however, there are also lots of unknowns.

One of the questions is whether the virus can be detected in urine with the same sensitivity for both mild and severe infections, stability is another question. RNA from various flaviviruses was shown to be stable at different levels in urine ranging from 2 days to 1 month at room temperature however, there seems to be a big variability between viruses [23-25]. We didn't encounter information specifically for YFV RNA stability. Further knowledge gap is viremia during asymptomatic/very mild infection and the kinetics of detectability in urine and blood. Naturally infected patients detailed in this manuscript often had severe disease and kidney involvement was also often described. In fact, kidney injury was found to be a risk factor associated with higher mortality following YFV infection [26,27]. Other members of the *Orthoflavivirus* genus e.g. dengue, Zika and West Nile viruses were also described to be clinically associated with kidney disease [28] however, underlining causes for kidney injury seems to be different amongst these viruses. Thus future studies are needed to understand these questions.

In several vaccine recipients, YFV RNA has been detected in urine. In endemic regions this detection, if the RT-qPCR does not distinguish the wild type from the vaccine strain, could be misinterpreted as a confirmed case and could trigger a false positive notification. Especially if the detection occurs when also a reactive vaccination campaign is carried out. Therefore, knowing (recent)vaccination history is important for both molecular and serological testing, but this is often enough not available in practice. Laboratory guidelines should clearly describe the possibility of vaccine-viral RNA detection post-vaccination, and recommend the use of RT-qPCRs which can distinguish between wild type and vaccine strain in recent vaccines [6], at least as confirmatory PCR.

Vaccine adverse events with the YF vaccine are extremely rare, 0–0.21/100,000 doses of vaccine [29], nevertheless they occur. Comparing healthy vs. VAE vaccines, it seems that virus is present in urine till later time points in VAE patients however, not all VAE patients had viral RNA in the urine. Given this, urine also could be added as a secondary specimen besides blood in the WHO guideline to the recommended specimens for viral detection in YF VAE investigations.

In general, other specimens than blood should be more often considered for arbovirus diagnostics. Besides urine, breast milk, semen and saliva were also investigated in YF studies [30,31], for other *Orthoflaviviruses* [22,32] and chikungunya [33]. For Zika virus, the risk of sexual transmission is well established [34]. Tick borne encephalitis-[35], chikungunya [36] and Zika viruses [37] have been detected in breast milk in a handful of studies. The correlation of detectability between blood, urine, and other specimens could not be assessed, due to the low number of studies investigating this. The observation shows that these samples could also represent a risk for disease transmission, thus awareness both amongst healthcare workers and population at risk should be raised.

Given the presence of YFV RNA in urine, wastewater could also be considered as an alternative sample for disease surveillance. Flavi-and other viruses were shown to be detected in wastewater [38,39]. The utility of wastewater sampling for YFV surveillance needs further evaluation tough.

This review has several inherent limitations. Conclusions were drawn from a very small number of articles but the total number of patients is quite high and allows to provide sound information on the added value of urine. The articles describing varied patient populations, with different disease severity, from different parts of the world, different specimens and schedules. The included articles used various PCR methods, cutoffs and targets and input volumes which might have influenced the detection length and viral load/PCR Ct value. For naturally infected individuals, viral load was mostly presented as RT-qPCR Ct values which cannot directly be correlated across the various RT-qPCR platforms/methods/volumes used in the studies. Similarly, comparison

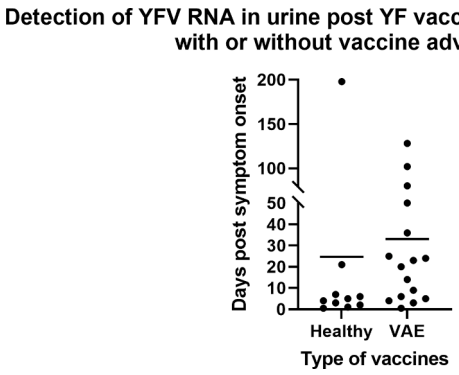

Fig. 3. Detection of YFV RNA in urine post YF vaccination amongts both healthy vaccinees and patients with VAE.

of viral load levels and kinetics between urine and blood was not done from a matched set of samples; some were longitudinal samples from one patients, others were samples at one time point from a patient group with or without comparison to blood. The differences regarding virus shedding in urine between the different genetic lineages of YFV has not been investigated. Due to the low number of available studies, statistical analyses have limited value. On top of all this, four papers published overlapping dataset, best attempts were made to separate the data to avoid duplication. All this might have skewed some of the analysis.

Despite these limitations, based on the preliminary evidence collated in this review, we would recommend urine as a standard specimen for YF molecular diagnostics and sequencing alongside but not instead of blood. Urine seems especially useful for late detection of the virus post-onset or vaccination.

Ethical statement

Obtaining ethical approval was not necessary as this review article used publically available information.

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Data availability

All data is available upon request.

CRediT authorship contribution statement

Zsofia Igloi: Writing – original draft, Methodology, Formal analysis, Conceptualization. **Laura Pezzi:** Writing – review & editing, Conceptualization. **Remi N. Charrel:** Writing – review & editing, Methodology, Conceptualization. **Marion Koopmans:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jcv.2024.105740.

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