Arbovirus, transmission sexuelle & appareil reproducteur masculin

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Overview

1. Brief introduction on viral infections in the male genital tract (MGT) and their consequences
2. The case of Zika virus in the human male genital tract
3. What evidence for other arboviruses in humans and animals? detection in MGT and sexual transmission
4. Conclusions and key issues

Arboviruses: vector-borne transmission of course… what else?

Arthropod-borne viruses (arboviruses) : primarily transmitted by cycles in hematophagous arthropods (mosquitoes, ticks…) and vertebrate hosts. However, non-vector-borne transmission can occur.

For several arboviruses, cases of inter-human transmission through :

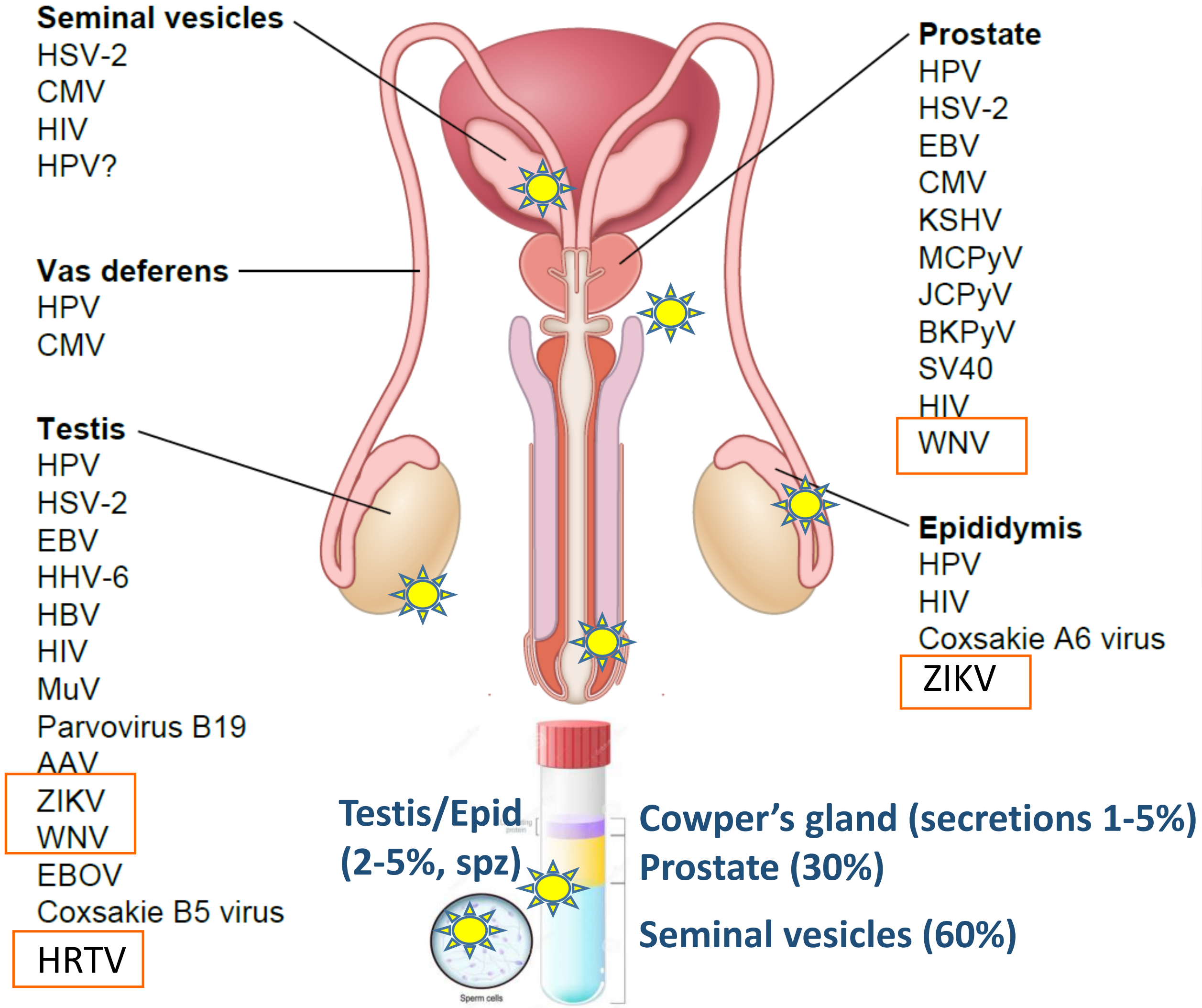
- Organ transplantation, blood transfusion and needle-stick injury
- Breast-feeding
- Intra-uterine transmission
- Inhalation of aerosols
- Direct contact with infected animals or animal products
- **Sexual transmission**

Zika virus : most widely recognized sexually-transmitted arbovirus
Increasing number of other arboviruses detected in the urogenital tract/sexual secretions of vertebrate hosts, along with case reports of sexual transmission

Issue: non vector-borne transmission difficult to detect in endemic areas & impact on epidemic hard to measure

A wide range of viruses are found in men genital tract (MGT)

- **In men, 38 viruses** from 18 distinct viral families **detected in genital organs and/or in semen**
- **15 can be sexually transmitted**



Seminal excretion of:

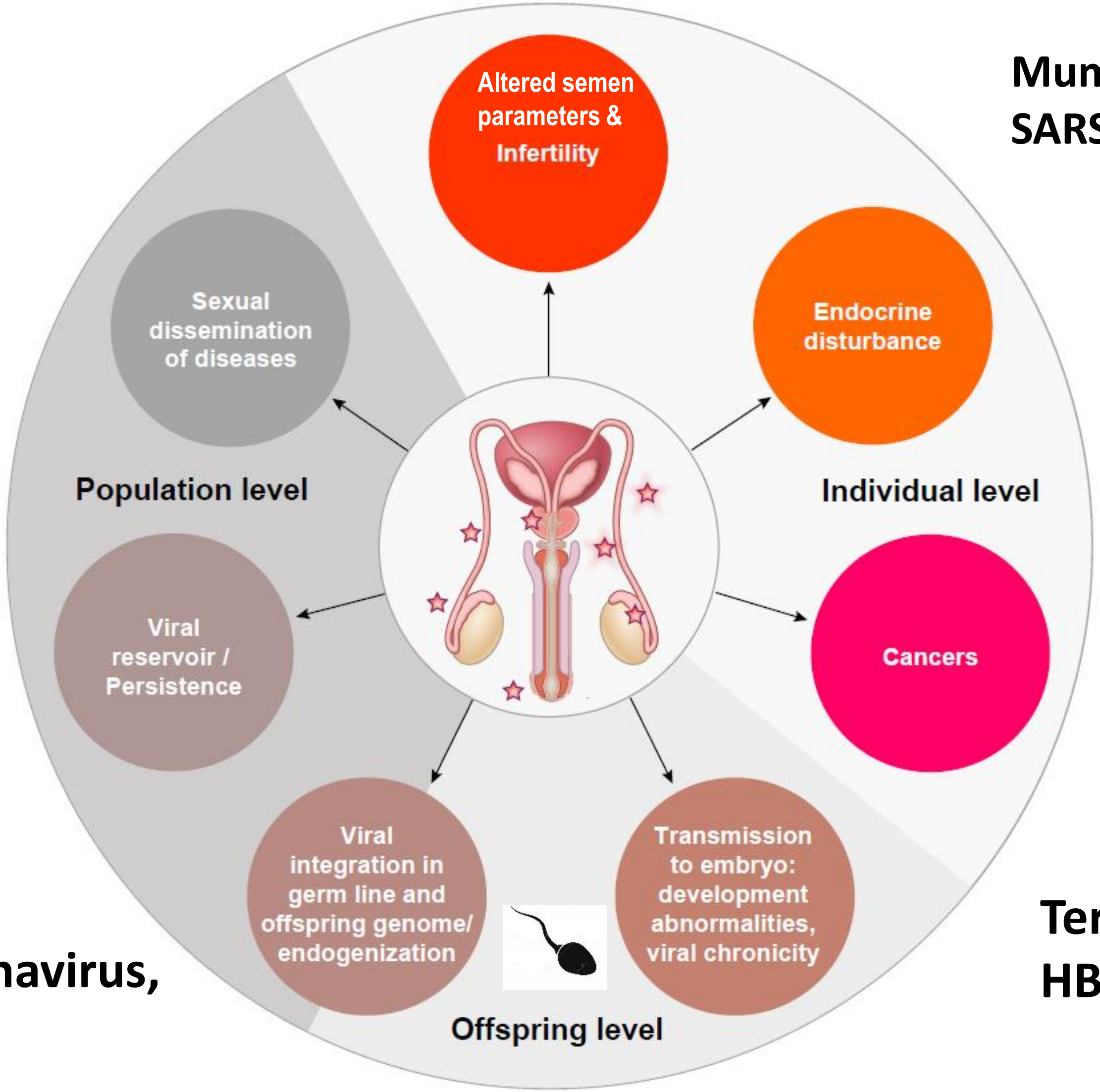
- **Genital** (HSV, HPV) **and systemic chronic viruses** (HIV, HBV, EBV, CMV, AAV, HCV, HHV6, HHV7, HTLV, KSHV,…)
- **Emerging (arbo)**viruses: **ZIKV,** Ebola and increasing reports for **CHIK, DENV, WNV, YFV, RVFV,** MARV, ANDV…

Le Tortorec…Dejucq-Rainsford, Physiol Rev 2020
« The odyssey of viruses in the male genital tract »

Viral infections and the male genital tract (MGT): what consequences?

HIV, HBV, HPV, HSV, …

Mumps virus, emerging viruses (ZIKV, SARS-CoV-2…)



ZIKV, Ebola,…other emerging viruses?

Papillomaviruses…

Endogenous retroviruses (8% of our genome), Bornavirus, HHV6…

Teratogenic Zika virus, HBV…

➢ **Deleterious consequences at 3 levels: individual, offspring and population**

Le Tortorec..Dejucq-Rainsford, Physiol Rev 2020

Sexual transmission of arboviruses: the case of Zika virus

Sexual transmission of arboviruses: the case of Zika virus

- **Teratogenic flavivirus** transmitted by Aedes mosquitoes, associated with miscarriage/microcephaly and Guillain-Barré syndrome in some adults
- **First suspected case of sexual transmission in 2011**, upon return from Senegal of an american scientist who contaminated his wife (*Foy, Emerging Infect Dis 2011*)
- **Large outbreak in the Americas in 2015-2016 (Asian genotype)**: case reports of **sexual transmission in 14 countries outside endemic area** (*D'ortenzio, NEJM 2016…)*

- **Sexual transmission reported up to 41 dpo, and infectious virus rescued from semen up to 69 dpo**
- **ZIKV RNA in semen from 61% of 39 symptomatic men within 30 dpo (36% in asymptomatic) and 33% of 184 men with median time of collection at 42 dpo (median VL 5,6 log RNA/ml)** *(Mead, NEJM 2018; Musso, CMI 2017)*. **VL up to 10 log RNA/ml and detection up to 414 dpo** (*Joguet, LID 2017*; *Bujan, LID 2020*)

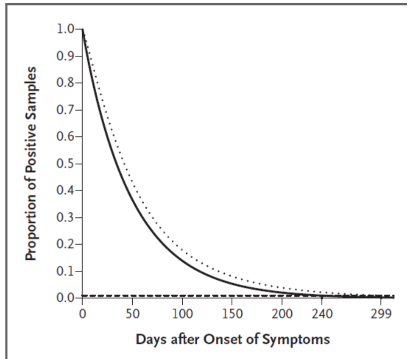
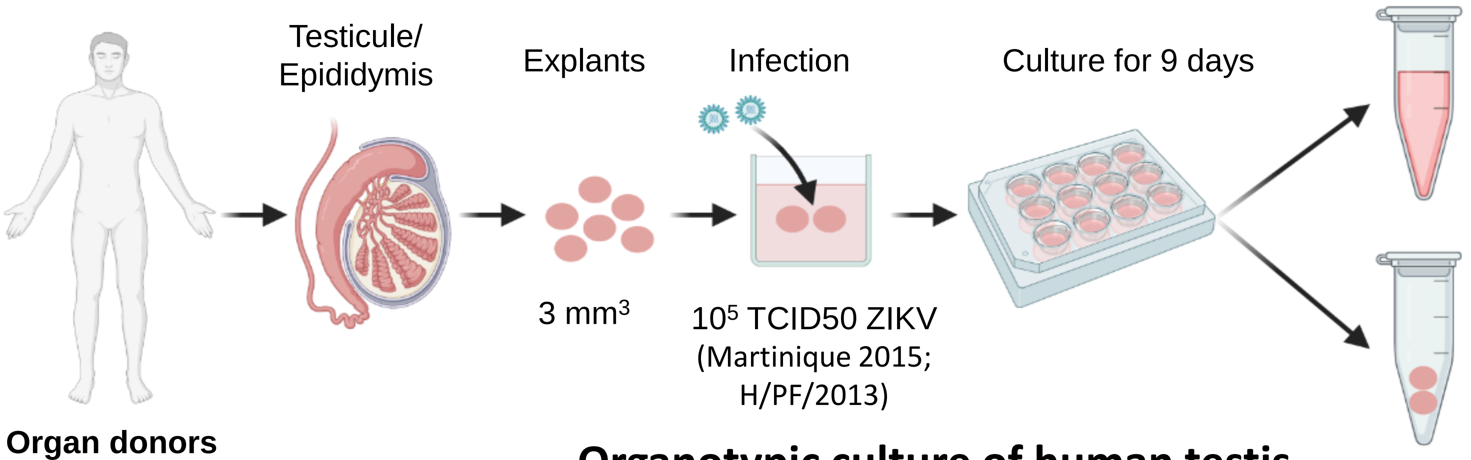


Figure 2. Estimated Proportion of Semen Samples Positive for ZIKV on RT-PCR, According to Days since Illness Onset.

- Male to female sexual transmission in mouse model **enhanced** viral dissemination in the female genital tract and **transmission to the foetus** (*Duggal et al, Plos Pathogens 2018*).
- ZIKV associated with human **spermatozoa up to 56 dpo** (Mansuy, LID 2016) and **infectious at 7 dpo** (*Joguet, LID 2017*)
- **Transient alteration of semen parameters**, restored after 4 months in symptomatic men (*Joguet, LID 2017; Huits, Bull World health organisation 2017*)

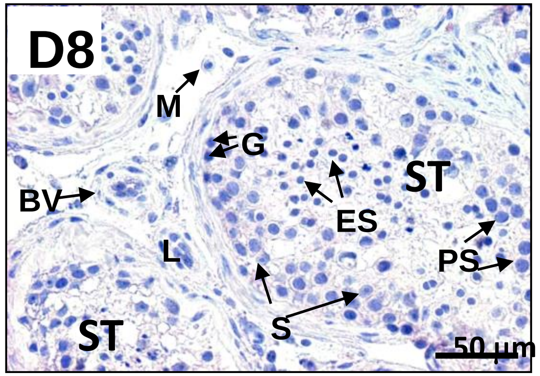
Le Tortorec..Dejucq-Rainsford, Physiol Rev 2020

Origins of Zika virus in human semen?



Organotypic culture of human testis

(*Roulet, Human Reprod 2006; Am J Pathol 2006; Kristensen PNAS 2018*)



- Testis architecture preserved
- All testis cell types and hormonal secretions present until D12

Virological analyses

ZIKV RNA (RT-qPCR)

TCID$_{50}$ on Vero

Infected cells: IHC and RNAScope

Testis morphology and functions analyses

Histology/cell markers expression (IHC, RT-qPCR)

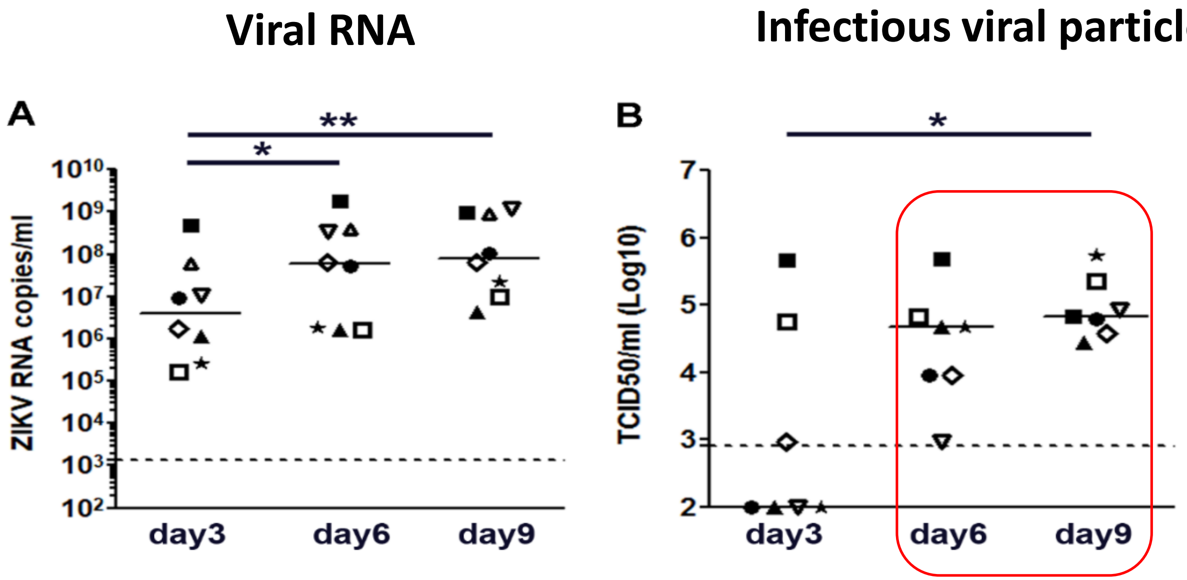
Hormone production, Apoptosis…

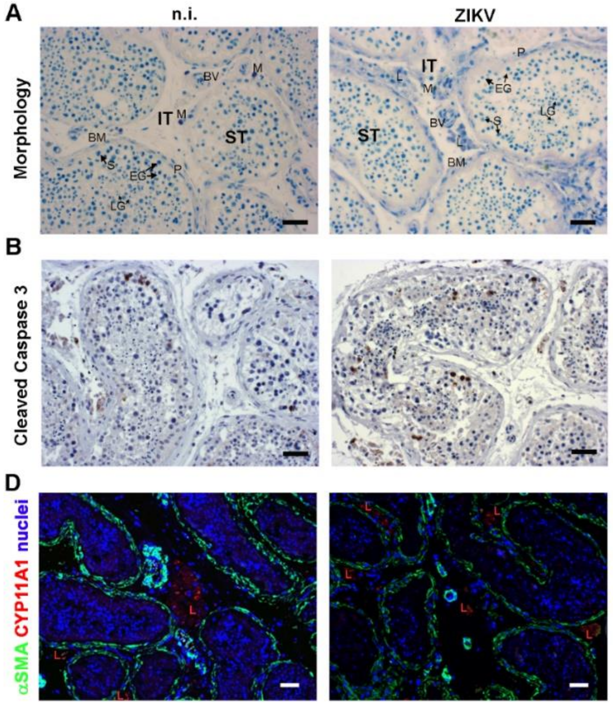
Innate response analyses

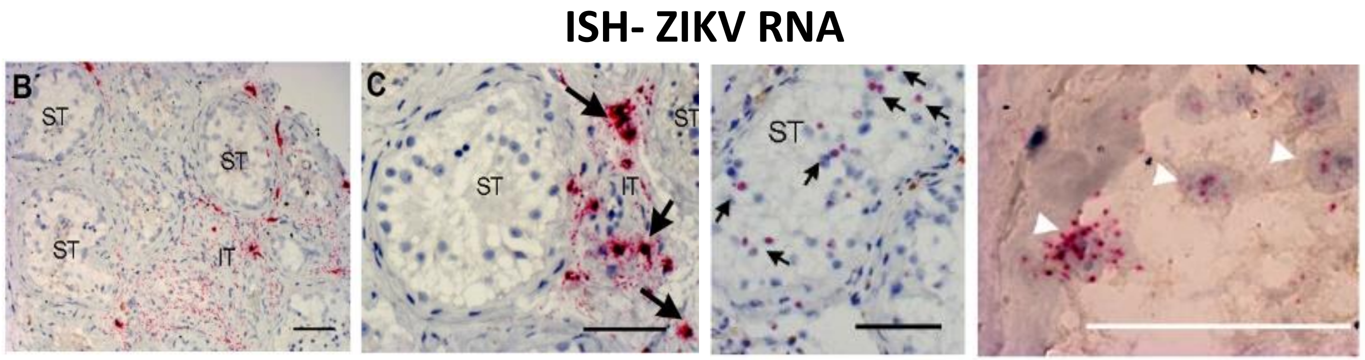
Cytokines and antiviral effectors

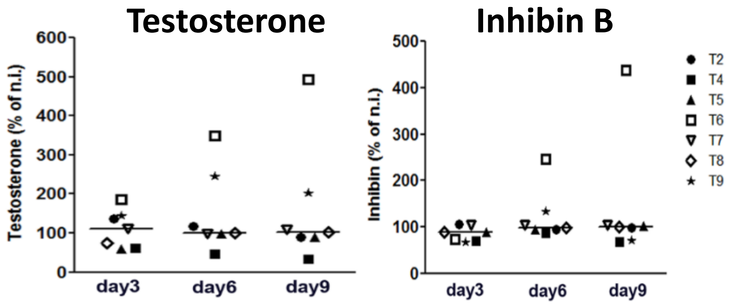
(RT-qPCR array and Legendplex)

Zika virus infection of human testis?





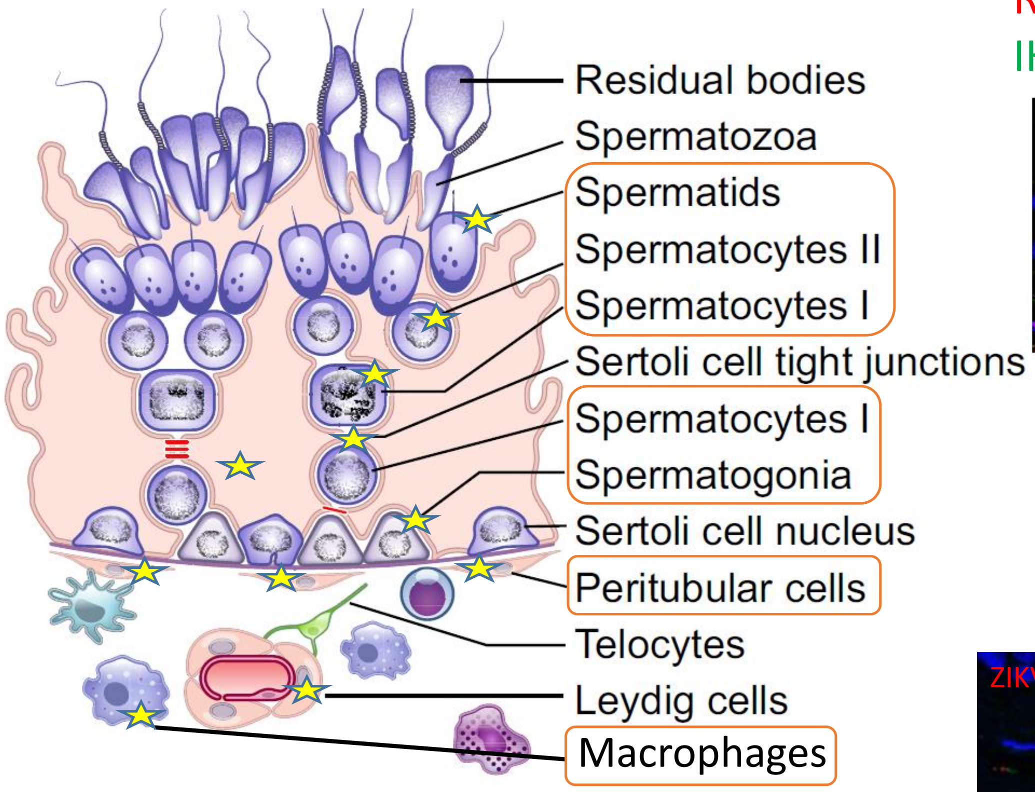




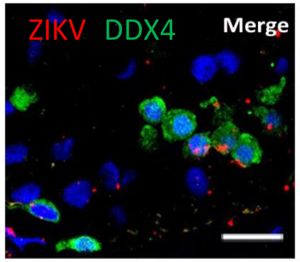
- ✓ ZIKV replicates *ex vivo* in the human testis, in interstitial tissue and seminiferous tubules
- ✓ No major deleterious effect on testis morphology and hormonal functions

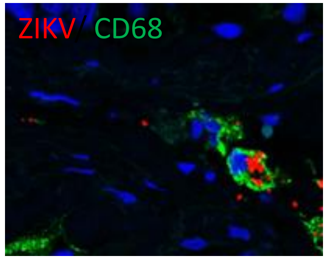
Matusali et al, J Clin Invest 2018

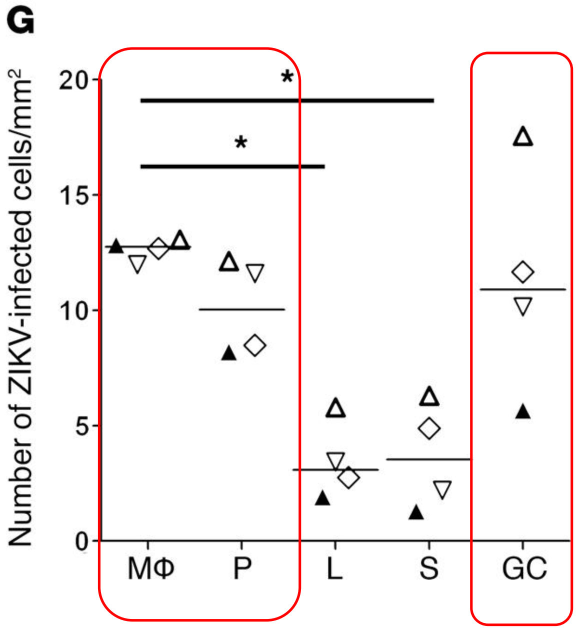
Target cells of Zika virus in the testis *ex vivo*?



RNAScope ZIKV/
IHC cell markers





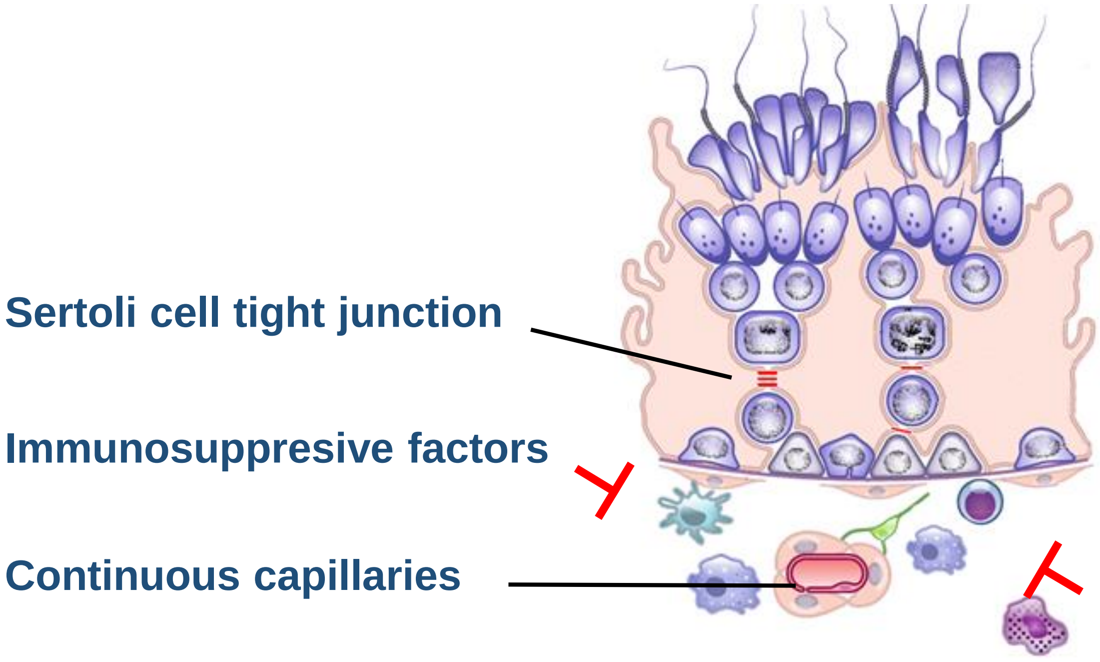


✓ **ZIKV primarily infects resident macrophages, peritubular cells and germ cells**

Matusali et al, J Clin Invest 2018

The human testis: a key reservoir for persistent viral excretion in semen?

- **The testis is an immune-privilege organ:** restricted access for immune cells and antibodies to protect germ cells from non-self recognition → systemic immune response/ orchitis induce testis damage and impair fertility

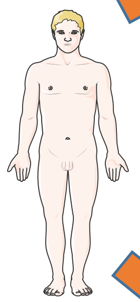


→ **Impairs viral clearance by systemic immunity**,
unless immune priviledge broken by inflammation/ immune infiltrates (eg Mumps virus)

- **Antiviral/pro-inflammatory innate response to ZIKV in the testis?**

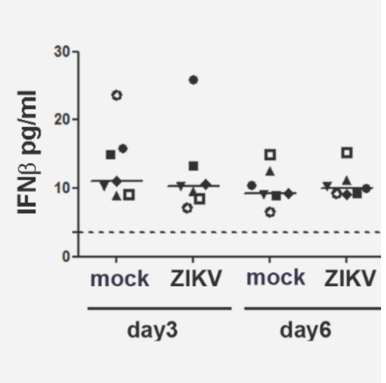
Weak innate response of the human testis to Zika virus

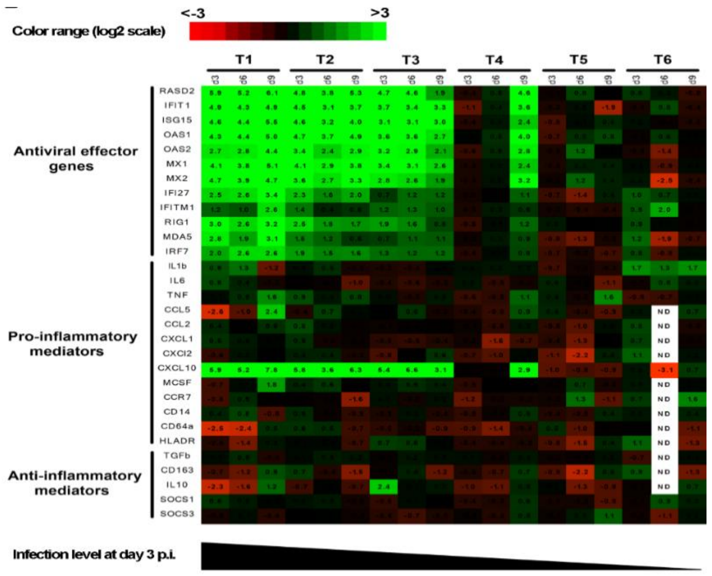
Testis response to infection *ex vivo*

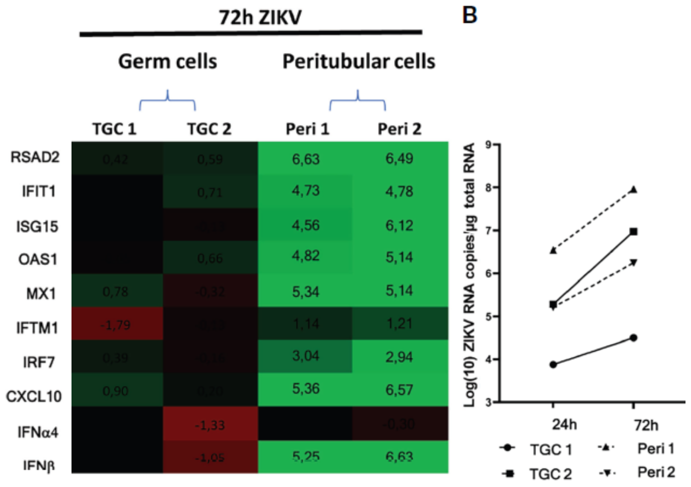


Post-mortem donors

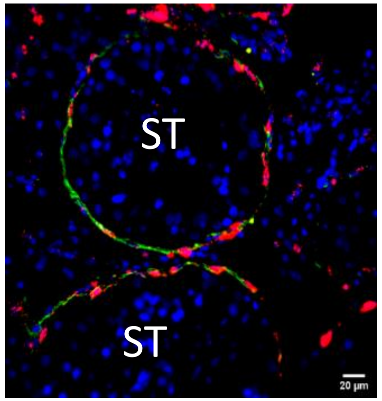
Germ cells response to infection *in vitro*







Antiviral RSAD2 / αSMA+ peritubular cells



Testis exposed to ZIKV

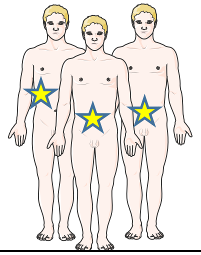
- **No IFN up-regulation + minimal pro-inflammatory response** (≠ mumps virus)
- Up-regulation of antiviral effectors correlates with higher infection and fails to control replication in the absence of IFN priming
- **No antiviral response by Zika-infected germ cells = ideal viral reservoir ?**

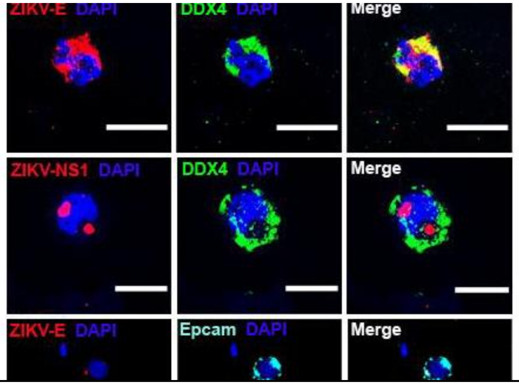
Matusali et al, J Clin Invest 2018
Kuassivi et al, Front Immunol 2022

Origin of prolonged excretion of ZIKV in human semen?

ZIKASPERM- Collab CECOS Pointe à Pitre et CHU Toulouse

ZIKV-infected men
Semen analysis up to 160 days post-symptoms





Testicular germ cells in semen are infected up to 5 months

The human testis is an important reservoir for Zika virus

- ✓ **In semen, the majority of ZIKV infected cells are testicular germ cells** (median 53% of infected cells, range 38-69)
- ✓ **Germ cells are persistently infected for the longest duration (5 months)**

Mahé et al, Lancet Inf Dis 2020

What evidence for other arboviruses in the male genital tract?

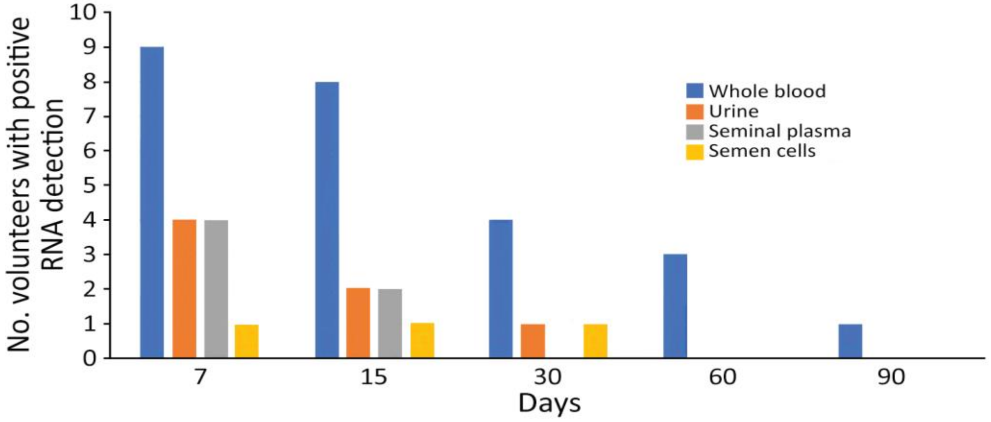
Dengue virus (DENV): mosquito-borne (Aedes), > 55% population exposed worldwide, endemic in >100 countries, increasing cases in France. Mostly mild form/asymptomatic but can be severe illness

- **Suspected sexual transmission**: 1) **woman to man** in South Korea in 2013 (*Lee, Infect Dis 2019*); 2) in **MSM** returning from Cuba and Puerto Rico to Spain in 2019 (transmission during incubation period). Identical DENV sequence in their semen (*Liew, J Travel Med 2020*).
- **DENV RNA** detected by RT-qPCR in **vaginal secretions** from a woman returning from Sri Lanka up to **18 dpo** (*Iannetta, Euro Surveill 2017*) and in **semen** of a man returning from Thailand up to **37 dpo** (Ct 24-31.8)(*Lalle, Euro Surveill 2018*). **Presence of negative-sense DENV RNA** indicative of virus replication in semen but **no infectious virus** rescued. In another study, no DENV RNA detected in semen of 5 men from Singapore with acute infections (*Molton, J Travel Med 2018*).

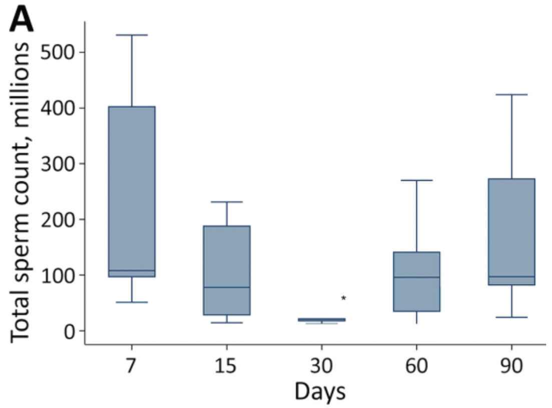
Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 28, No. 6, June 2022

Effects of Acute Dengue Infection on Sperm and Virus Clearance in Body Fluids of Men

Joffrey Mons, Dominique Mahé-Poiron, Jean-Michel Mansuy, Hélène Lheureux, Delphine Nigon, Nathalie Moinard, Safouane Hamdi, Christophe Pasquier, Nathalie Dejucq-Rainsford, Louis Bujan



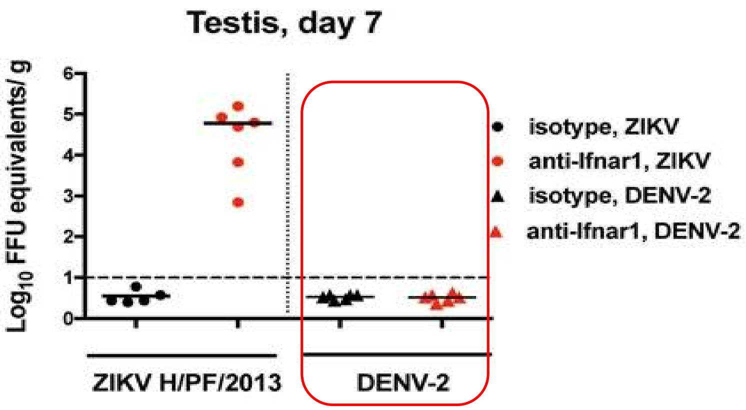
10 **DENV-2** infected men with mild symptoms from La Réunion: **4/10 with DENV RNA in semen at 7 dpo; seminal excretion up to 30 dpo** (semen Ct 33-41; blood Ct 28-42). **Low level of infectious virus at 7 dpo (2/4). No virus in spz.**



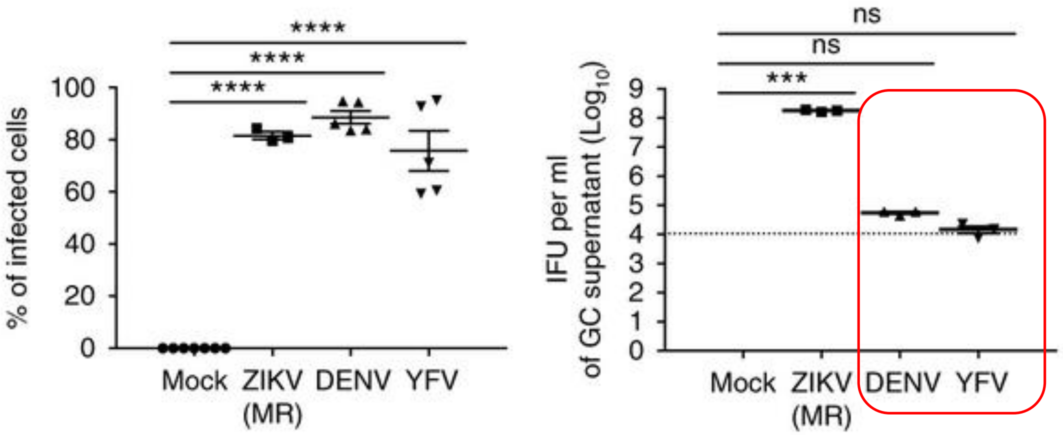
Sperm production transiently decreased at 30 dpo: Fever? Genital organs infection?

- **In mouse models, DENV failed to productively infect testicular cells** (*Govero, Nature 2016; Ma, Cell 2016; Robinson, Nat Com 2018; Shen, Front Cell Infect Microbiol 2017*).

IFN-deficient mice infected in vivo *(Govero, Nature 2016)*



In vitro infected mouse testicular germ cells- *72h pi (Robinson, Nat Com 2018)*



- **DENV3 RNA** in **prostate and seminal vesicle** from pig-tailed macaques **but not testis** (PCR) (Pamungkas, Microb Ind 2011; Prabandari, Int J Sci 2017)

➢ **No/abortive replication of DENV in human testis *ex vivo*** (our unpublished data)

No experimental elements in favor of DENV replication in testis
So far, DENV appears poorly infectious in semen, vRNA not detected beyond 30 dpo, with only rare cases of suspected sexual transmisison reported despite high prevalence worldwide.
The excretion of DENV in genital secretions/ evolution needs to be explored in larger cohorts, and at distance from infection in severely-ill patients

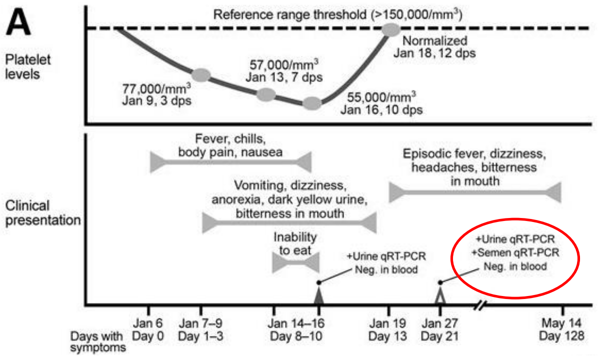
West Nile Virus (WNV): mosquito-borne (Culex), 80% asymptomatic, 3-7% case fatality rate in the US since 1999, increasing in France mainland

- One **suspected male to female sexual transmission** during incubation period in endemic US in 2014 (*Kelley, J La State Med Soc 2016*).
- RT-qPCR on semen (*Gorchakov, Int J Mol Sci 2019*)**: positive semen sample at 22 dpo in 1/3 patients collected 9-34 dpo**. Issue of vRNA degradation in frozen samples during storage.
- **WNV antigen detected in post-mortem testis** (seminiferous tubules++ and inflammation ++ in interstitial tissue) **and prostate** of one immunocompromised patient at **14 dpo** (*Armah, Brain Pathol 2007*)
- Detection in testis by EM (*DeSalvo, Transplantation 2004; Smith, Human Pathol* 2004)
- **Mice inoculated by the vaginal route developed fatal WNV infections** (*Burke, Immmunol Cell Biol 2004*)

Potential for WNV to infect the male genital tract and be transmitted through semen ?

Yellow Fever virus (YFV): mosquito-borne (Aedes), asymptomatic to severe, endemic in several African and South American countries

- **YFV RNA** : **2 patients** (resident and dutch traveler from Brazil) with **low level excretion in semen at 21 dpo** (Barbosa, Emerg infect Dis 2018) and **up to 43 dpo** (Phan, Open Forum Infect Dis 2020). **VL at earlier time point unknown**



Patient 1
Day 21:
Semen: **Ct 31.00**, 5×10^2 RNA copies/mL
Urine Ct 28.57, 3.3×10^3 RNA copies/mL
Blood neg

Patient 2
Day 30:
Semen: **Ct 33.5**
Urine Ct: 34.7 (Ct 15 at D7)

- YFV replicated in commercial Sertoli cells (*Siemann, J Virol 2017*) but not in mouse testicular germ cells (*Robinson, Nat Com 2018*)

➢ ***Two other zoonotic Flaviviruses are present in the animal UGT and sexually transmitted:***

Japanese Encephalitis Virus (JEV): humans, horses, pigs

- JEV persisted in **semen** of experimentally infected boar for **17 days** and **female recipients became infected after artificial insemination** (*Habu, Uirusi 1977*).
- JEV infects and cause inflammatory changes in the **testes of JEV-infected boars** (*Zheng, Vet Microbiol 2019*)

Tick-borne encephalitis virus (TBEV): humans, rodents and other wild or domestic mammals, increasing in Europe
Naïve **female mice became infected with TBEV after mating with infected males**, with viral RNA detected in embryonal tissues of 2/11 litters (*Gerlinskaia, Biull Eksp Biol Med 1997*)

Togoviridae family, *Alphavirus* genus

Chikungunya virus (CHIKV): mosquito-borne (Aedes), cause of severe, debilitating and often chronic arthralgia in humans.

- CHIKV RNA detected up to **30 dpo in semen** of a patient from Brazil with a concurrent DENV-3 infection reporting burning sensation in genital region (*Bandeira, IDCases, 2016*)
- In a Brazilian cohort study, detection of **CHIKV RNA in 6/42 (14%) semen samples, up to 56 days**, and 20/99 (20%) vaginal secretions samples (median time for loss of detection 25 dpo) (*Martins, PLoS Negl. Trop. Dis. 2022*).
- CHIKV **transiently decreased testosterone with unchanged LH** in infected men from Martinique (*unpublished data, collab A. Cabier*)

➢ **In animals, three *Alphaviruses* are present in the MGT and sexually transmitted**:

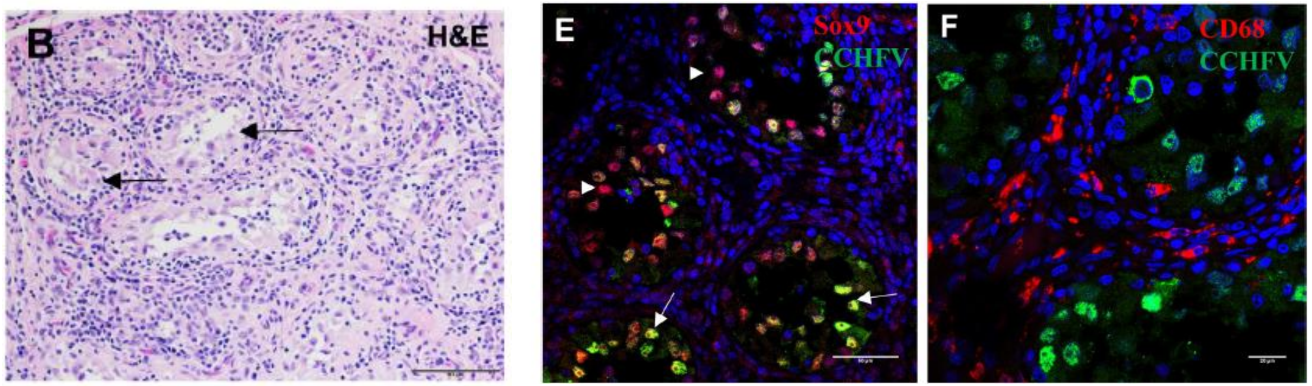
- Zoonotic Eastern equine encephalitis virus (EEEV) and Highlands J virus (HJV) detected in **semen** of domestic turkeys 4-5 days post-infection (*Guy, Avian Dis 1995*) and **recovered in hens inseminated with virus-contaminated semen** (1/10 and 3/10, respectively).

- Venezuelan equine encephalitis virus (VEEV) replicated in testes from golden hamster and was **sexually transmitted to female** from seroconverted male inoculated by intratesticular route (*Vestergaard, Am J Pathol 1971*)

Nairoviridae family, *Orthonairovirus* genus:

Crimean-Congo hemorrhagic fever virus (CCHFV): tick-borne pathogen that can cause fatal hemorrhagic fever in humans (Africa, Asia, south Europe).

- **5 cases of suspected sexual transmission of CCHFF from men** (convalescent or before illness) to wives since 1999 in endemic countries (Iran, Turkey, Russia) (see *Blitvich, Viruses 2020)*
- Unilateral **epididymo-orchitis** in a patient 4 dpo
- **CCHFV RNA found in urethral (9 dpo) and vaginal (11 dpo) swabs** from CCHF patients (*Yagci-Caglayik, Euro Surveill 2020*). Viral RNA copy numbers in genital swabs > sera collected same day.
- CCHFV **persisted in the testes of experimentally-infected cynomolgus macaques** (*Smith, Plos Pathog 2019*):
    - Unilateral inflammation in the testis (3/4 animals) and atrophy (1/4)
    - **Viral RNA and antigen in Sertoli cells at 30 dpo, absent in macro** (1/3)



Interactions of CCHFV with genital tract requires attention

Nine arboviruses have been detected in the human genital tract

Virus	Suspected human sexual transmission cases	Viral material detection and duration	Infectious virus rescued	Replication during experimental infection
Zika virus	Many M to W (> 14 non-endemic countries)	Semen (**414 dpo**), Testis, Epid	**S (69-90 dpo)**	IFN deficient mice testis & epid NHP testis +/-, seminal vesicle Human testis and epid ex vivo
Dengue Virus	1 W to M in South Korea; 1 M to M in Spain	Semen (**37 dpo**), Vagina (18 dpo)	**S (7 dpo, weak)**	Abortive infection in mouse and human testis
West Nile Virus	1 M to W in USA	Semen (**22 dpo**), Testis **(14 dpo)**	NT	Human testis *ex vivo* Parrots (ovary and testis)
Yellow Fever Virus	0	Semen (**21 dpo**)	NT	NT
Chikungunya Virus	0	Semen (**30 dpo**)	NT	Human testis ex vivo
Crimean-Congo Hemorrhagic Fever virus	5 M to W in Iran, Turkey, Russia	Testis (**NHP, 30 dpo**), Urethra (**9 dpo**), Vagina (11 dpo)	NT	NT
Rift Valley Fever Virus	0	Semen (**117 dpo**, immunodeficient)	No	NT
Heartland virus	0	Testis **post-mortem (10 dpo)**	NT	NT
Severe fever with thrombocytopenia syndrome virus	0	Semen (**30 dpo**)	NT	NT

In vertebrate animals, > 14 arboviruses with potential for sexual transmission

Suspected cases of human sexual transmission	Virus	Sexual Transmission between Laboratory Animals	Transmission by Artificial Insemination	Evidence of the Virus in the Reproductive Tract or Sexual Secretions of Vertebrate Animals: Virus Isolation		Evidence of the Virus in the Reproductive Tract or Sexual Secretions of Vertebrate Animals: Antigen Detection	Evidence of the Virus in the Reproductive Tract or Sexual Secretions of Vertebrate Animals: Nucleic Acid Detection	References
	Asfarviridae							
	African swine fever virus	NT	+ [a]	+ [a]	Pigs	NT	NT	[16]
	Bunyavirales							
	Aino virus	NT	NT	NT [b]		NT	NT	[43]
	Akabane virus	NT	NT	+	Cows	NT	NT	[42]
yes	Crimean-Congo hemorrhagic fever virus	NT	NT	–	NHP	+	+	[24]
	Schmallenberg virus	NT	NT	+	Bulls, goats, sheeps	NT	+	[35–40]
	Flaviviridae							
	Japanese encephalitis virus	NT	+	+	Pigs	+	NT	[132,133]
	Spondweni virus	NT	NT	+		NT	+	[87]
	Tembusu virus	NT	NT	+	Ducks	+	+	[135–138]
	Tick-borne encephalitis virus	+	NT	NT	Mice	NT	NT	[134]
yes	West Nile virus	NT	NT	NT	Parrots	+	NT	[130]
yes	Zika virus	+	NT	+	NHP, rodents	+	+	[90–127]
	Reoviridae							
	Bluetongue virus	–	+	+	Bulls, rams	+	+	[143–153]
	Rhabdoviridae							
	Bovine ephemeral fever virus	NT	NT	NT	Deers	NT	+	[156]
	Togaviridae							
	Eastern equine encephalitis virus	NT	+	+	Turkey	– [d]	NT	[161]
	Highlands J virus	NT	+	+	Turkey	NT	NT	[161]
	Venezuelan equine encephalitis virus	+ [c]	NT	+	Hamsters	+	NT	[163]

Blitvich…Foy, Viruses 2020

Updated list : 7 arboviruses in MGT of farm animals

Table 8. *Viruses that infect farm animal MGT*

Host	Viral Family	Virus	MGT Organs and Cells Infected	Seminal Excretion (S) and Persistence (S+)	Venereal Transmission (V), Reproduction Failure (R), Teratogen (T), Abortion (A), Embryo Death (E)
Swine	Anelloviridae	TTV	T (574)	S+ (347, 574)	
	Asfarviridae	ASFV*		S (680)	
	Circoviridae	PCV2[a]	T, E, SV, P, BG (250, 416, 574)	S (380, 416)	R
	Flaviviridae	CSFV*	T+ (germ cells), E+, VD+ (107)	S+ (108)	E
	Flaviviridae	JEV*†[a]	T (268)	S (400)	
	Flaviviridae	BVDV	T+[b], P+[b] (Mϕ), SV+[b] (Mϕ) (679)	S+[b] (679)	
	Flaviviridae	APPV		S (614)	
	Parvoviridae	PPV	E (248)	S (354)	V?; R
	Parvoviridae	PPV4		S (126, 216)	
	Herpesviridae	PRV	T, E, foreskin (274, 467)	S (453)	
	Paramyxoviridae	PoRV	T+, E+ (575, 650)	S+ (575)	R
	Arteriviridae	PRRSV	T (germ cells, macrophages), E, VD, SV, PR (Mϕ) (109, 632)	S+ (109)	V; R
	Coronaviridae	PEDV	(ND)	S (199)	V?
	Picornaviridae	PEV		S (544)	
	Picornaviridae	PTV		S (544)	
	Picornaviridae	FMDV		S (451)	
	Picornaviridae	SVDV[a]		S (451)	
	Hepeviridae	HEV†[a]		S (388)	
Bull	Flaviviridae	BVDV	T+ (Sertoli, germ cells, epithelial cells), P+, E+, SV+, U+ (epithelial cells, fibrocytes) (63, 238, 358, 504, 716)	S+[c] (63, 358)	R; E; T; A
	Flaviviridae	BDV		S (72, 208)	
	Peribunyaviridae	PEAV*	T (46)		
	Peribunyaviridae	SBV*		S+ (289, 549)	
	Herpesviridae	BHV-1	Penis, foreskin, U (518)	S (237)	
	Retroviridae	BLV		S (162, 237)	
	Retroviridae	BIV		S (495)	
	Poxviridae	LSDV	T+, E+ (24)	S+ (316)	
	Picornaviridae	FMDV		S (119)	
	Reoviridae	BTV*		S (706)	R; E; T; A
Sheep	Reoviridae	BTV*	T+, E, P, BG (endothelial cells) (560)	S+ (383)	E; A; T
	Phenuiviridae	RVFV*†[a]	T (endothelial cells, fibroblasts, smooth muscles, Mϕ) (514)		
	Retroviridae	MVV	T, E, SV, P, BG, AG (543, 595)	S (595)	
	Retroviridae	CAEV	T, E, VD, SV, P, BG (10, 699)	S (10)	
	Retrovirida	SRLV genotype E	T+ (255)		
Horse	Herpesviridae	EHV	T+ (endothelial cells, macrophages), E, P+ (epithelial cells) (294, 677)	S (10, 279, 677, 721)	A; E
	Arteriviridae	EAV	T, E+, VD+, AG+[d], P+, BG+, SV+	S+[d] (87, 293, 684)	V; R

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CONCLUSIONS

- **Accumulating evidence that several arboviruses can replicate in the reproductive tract, persist in semen and lead to cases of sexual transmission**
- **Persistence in semen demonstrates the existence of viral reservoirs in the male genital tract:** immuno-privilege testis but also other organs (see prolonged ZIKV excretion in vasectomized men).
- **Rare events non-epidemiologically relevant but may indicate viral evolution towards sexual transmission**
- **Sexual transmission may enhance arthropod-driven transmission in vector endemic/emerging regions, maintain endemicity and spread the disease outside the insect vector area**
- **Genital tract infection can impact reproductive health and affect pregnancy/embryo**

Further investigations required to :

- **determine potential for sexual transmission of emerging arboviruses, impact on reproductive health and medically-assisted reproduction to avoid partner & embryo contamination**
- **understand mechanisms underlying viral reservoirs**

Several issues to take into account for these studies…

Key points for better anticipation

- **Sexual transmission difficult to identify in insect vector regions:** more systematic semen screening in cohorts; longitudinal sampling to assess persistence and intermittent seminal excretion
- **Need to learn more from other vertebrate hosts (One health)**: ZIKV in human semen unexpected in 2015 but 5 arboviruses were already known to infect animal semen. > 80% of emerging viruses are zoonotic
- **Presence of viral RNA in genital fluids does not necessarily imply infectious virus/ viral load high enough for transmission**. But failure to rescue infectious virus does not mean no risk (issues with technique sensitivity, sample conservation…)
- **To assess infection and impact on the genital tract,** **animal models have a number of limitations**: **natural resistance** to the pathogen (eg mouse for ZIKV); **milder or stronger pathogenesis** (eg NHP semen less frequently infected by ZIKV); **failure to fully recapitulate human genital organs specificities** such as morphology, spermatogenesis duration, innate responses (e.g. ZIKV-induced orchitis specific to the mouse)
- **Need adequate *ex vivo* /animal models to assess replication in the genital tract as well as potential for sexual transmission through the recipient genital mucosa** (foreskin/urethra, vagina/cervix, rectum/colon) and modulating role of seminal fluid

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