INFEZIONE DA HEV: UPDATE EPIDEMIOLOGICO-CLINICO

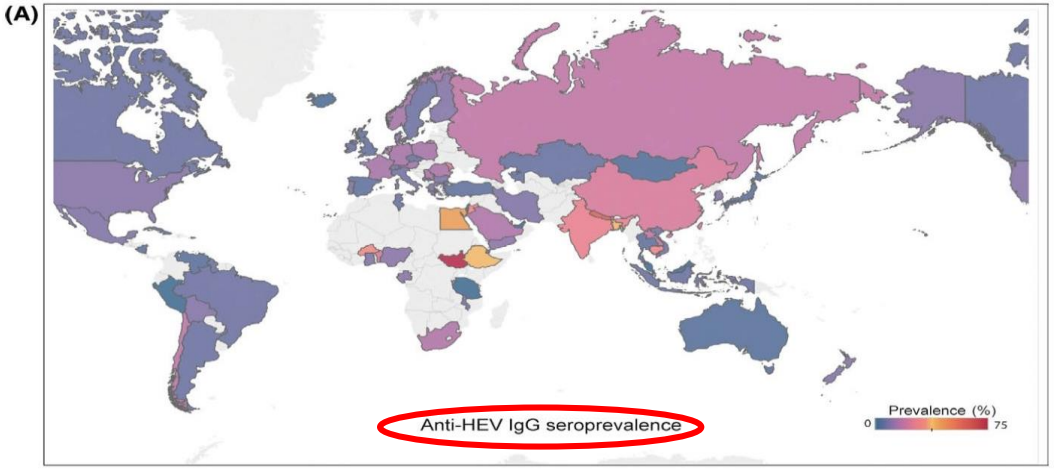
MARCO POZZI

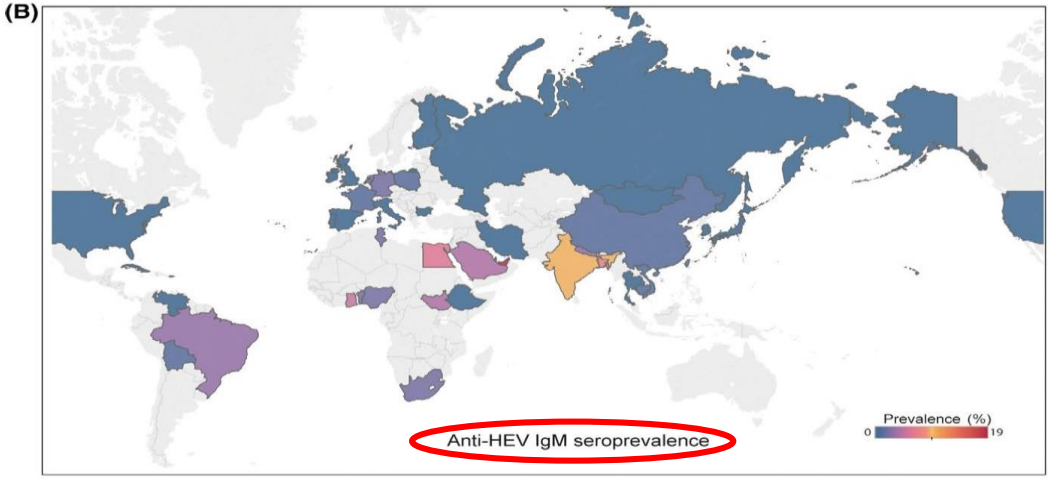
SOD MALATTIE INFETTIVE E TROPICALI

AOU CAREGGI - FIRENZE

EPIDEMIOLOGIA

- **SI STIMA CHE 1/3 DELLA POPOLAZIONE MONDIALE SIA STATA ESPOSTA AL VIRUS.**
- SI STIMA INOLTRE CHE OGNI ANNO 20 MILIONI DI PERSONE ACQUISISCANO L'INFEZIONE CAUSATA DAL VIRUS DELL'EPATITE E (HEV), CHE OLTRE 3 MILIONI PRESENTINO SINTOMATOLOGIA E CHE OGNI ANNO SI VERIFICHINO ALMENO 600 MILA DECESSI ASSOCIATI ALL'HEV.





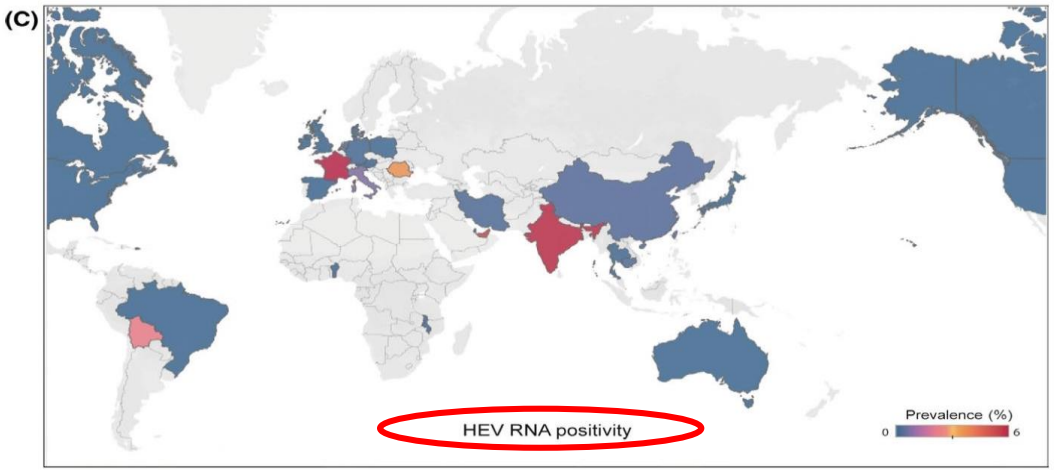


FIGURE 2 (A) The global seroprevalence of anti-HEV IgG antibody (B) The global seroprevalence of anti-HEV IgM antibody (C) The global prevelence of HEV RNA prositivity

Li, P., Liu, J., Li, Y., Su, J., Ma, Z., Bramer, W. M., … Pan, Q. (2020). *The global epidemiology of hepatitis E virus infection: a systematic review and meta-analysis. Liver*

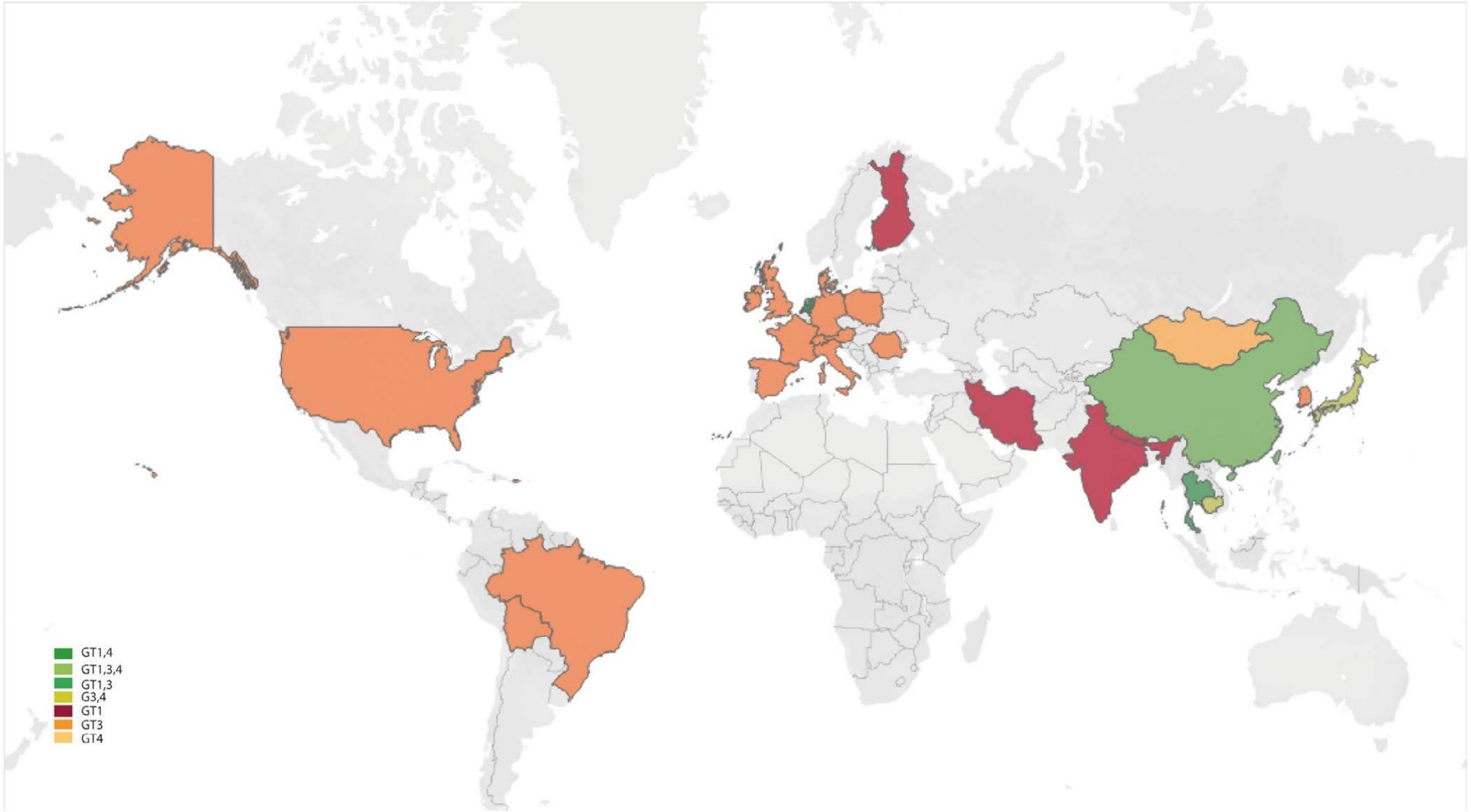


FIGURE 3 Hepatitis E virus genotype distribution in our study

Li, P., Liu, J., Li, Y., Su, J., Ma, Z., Bramer, W. M., … Pan, Q. (2020). *The global epidemiology of hepatitis E virus infection: a systematic review and meta-analysis. Liver*

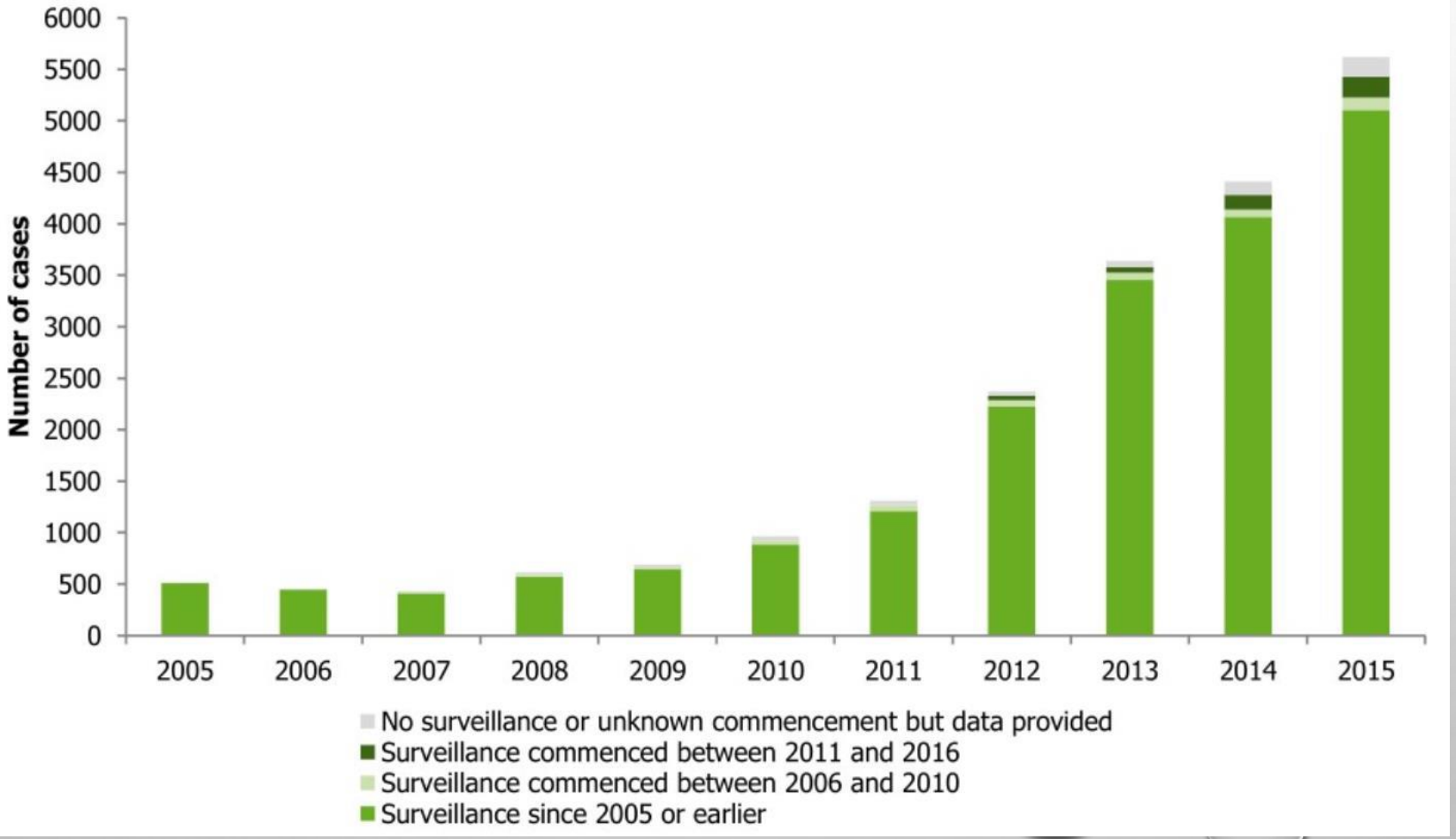
EPIDEMIOLOGIA EUROPA

- NEL 2017 È STATO PUBBLICATO DA PARTE DELL'ECDC UN REPORT SULLA SORVEGLIANZA **DELL'EPATITE E IN EUROPA RIFERITO AL DECENNIO 2005-2015.**
- IN 20 PAESI UE SONO ATTIVI SISTEMI DI SORVEGLIANZA E PROTOCOLLI CONSOLIDATI PER L'EFFETTUAZIONE DI TEST, MENTRE NEI RESTANTI NON VIENE ATTUATA UNA SORVEGLIANZA SPECIFICA; SONO STATE INOLTRE RISCONTRATE SIGNIFICATIVE DIFFERENZE NELLA DEFINIZIONE DI CASO E NEI CRITERI DI LABORATORIO, CLINICI ED EPIDEMIOLOGICI ADOTTATI.
- **I DATI EPIDEMIOLOGICI EUROPEI RISULTANO TUTTAVIA IN UNA PROBABILE SOTTOSTIMA LEGATA AL FATTO CHE L'EPATITE E NON È SOGGETTA A OBBLIGO DI NOTIFICA A LIVELLO UE, E LA PREDISPOSIZIONE DI PROGRAMMI SPECIFICI DI SORVEGLIANZA È A DISCREZIONE DEI SINGOLI STATI MEMBRI.**

IL 75% DELLE SEGNALAZIONI PROVIENE DA GERMANIA, FRANCIA E REGNO UNITO (CHE RAPPRESENTANO IL 41% DELLA POPOLAZIONE TOTALE IN UE), PAESI IN CUI IL SISTEMA DI SORVEGLIANZA NAZIONALE È ATTIVO ALMENO DAL 2005, OBBLIGATORIO IN GERMANIA E VOLONTARIO IN FRANCIA E REGNO UNITO

EPIDEMIOLOGIA

NUMERO DI CASI CONFERMATI ALL'ANNO DI EPATITE E DAL 2005 AL 2015 IN EUROPA



EPIDEMIOLOGIA
ITALIA

E' GIUSTO PERÒ SOTTOLINEARE CHE :

UNA INIZIALE VALUTAZIONE EFFETTUATA NEL 2016 SU UN PICCOLO CAMPIONE DI DONATORI ABRUZZESI AVEVA SOLLEVATO UN CERTO ALLARME, DAL MOMENTO CHE ERANO STATE OSSERVATE DUE DONAZIONI VIREMICHE SU UN TOTALE DI 313 ESAMINATE, CON UNA PREVALENZA DI IGG ANTI-HEV DEL 49% .

AL CONTRARIO STUDI PIÙ RECENTI (MULTICENTRICI) ESEGUITI SU 10.000 DONATORI DI SANGUE RESIDENTI IN NORD ITALIA, INDICANO PREVALENZE DI VIREMIA E DI REATTIVITÀ ANTICORPALE BEN PIÙ CONTENUTE ED ASSIMILABILI AI PAESI OCCIDENTALI A PIÙ BASSA ENDEMIA.

(HEV RNA 1 SU 10.000, IGG ANTI HEV 9.7%).

EPIDEMIOLOGIA
SEIEVA

- **UNA CRITICITÀ LEGATA ALLA SORVEGLIANZA DELL'HEV È LEGATA AD UN ALTO LIVELLO DI SOTTONOTIFICA ATTRIBUIBILE NELLA MAGGIOR PARTE DEI CASI AD UNA CONOSCENZA ANCORA LIMITATA SULL'INFEZIONE.** TALE CRITICITÀ È LEGATA PRINCIPALMENTE AL FATTO CHE NON VI È ANCORA COMPLETA CONSAPEVOLEZZA SUL RUOLO DELLE **INFEZIONI AUTOCTONE NELL'EPIDEMIOLOGIA DELL'INFEZIONE**, E SI TENDE AD ASSOCIARLA PREVALENTEMENTE A VIAGGI ALL'ESTERNO IN AREE ENDEMICHE. CONSEGUENTEMENTE, LA RICERCA DEL VIRUS VIENE DIFFICILMENTE EFFETTUATA SU SOGGETTI CHE NON SONO VIAGGIATORI, ANCHE NEI CASI IN CUI SAREBBE INDICATO.
- **I DATI RACCOLTI DAL SEIEVA MOSTRANO INOLTRE COME DAL 2007 AD OGGI, SOLO NEL 38% DEI SOGGETTI CON EPATITE ACUTA RISULTATA NEGATIVA ALLA RICERCA DEL VIRUS A, B E C (QUINDI CASI POSSIBILI DI EPATITE E), VIENE EFFETTUATA UNA RICERCA SPECIFICA PER IGM ANTI EPATITE E.** NEI SOGGETTI IN CUI TALE RICERCA È STATA EFFETTUATA, È STATA OTTENUTA UNA POSITIVITÀ PER HEV PARI AL 75%, A DIMOSTRAZIONE DELL'ALTA PREVALENZA DELLA MALATTIA.
- SI STA TUTTAVIA RISCONTRANDO UNA CRESCENTE CONSAPEVOLEZZA DA PARTE DELLE FIGURE MEDICHE, IN QUANTO LA PERCENTUALE DI CASI "POSSIBILI" TESTATI È IN AUMENTO E **NEL 2018 È STATA SUPERIORE AL 60%.**

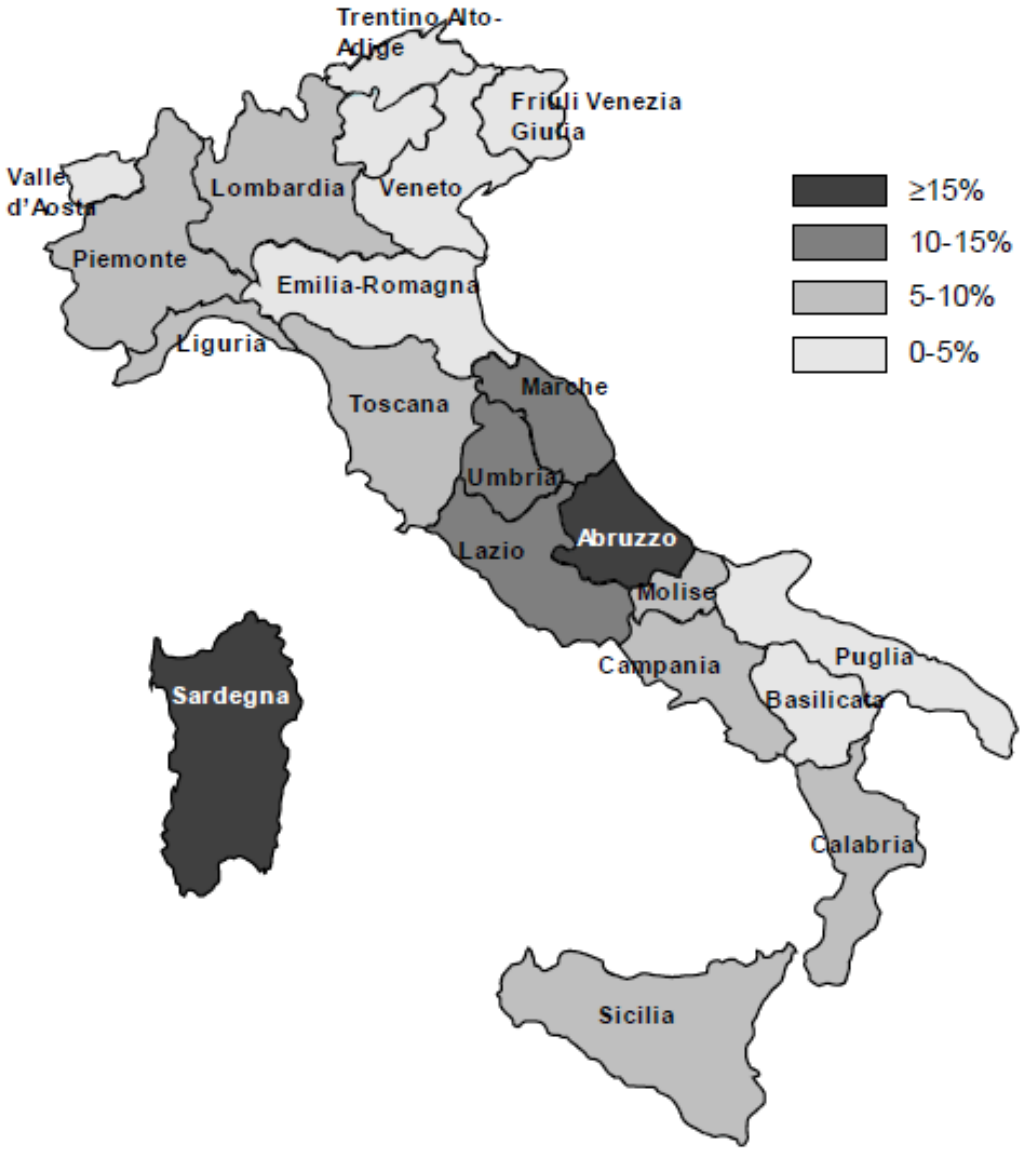
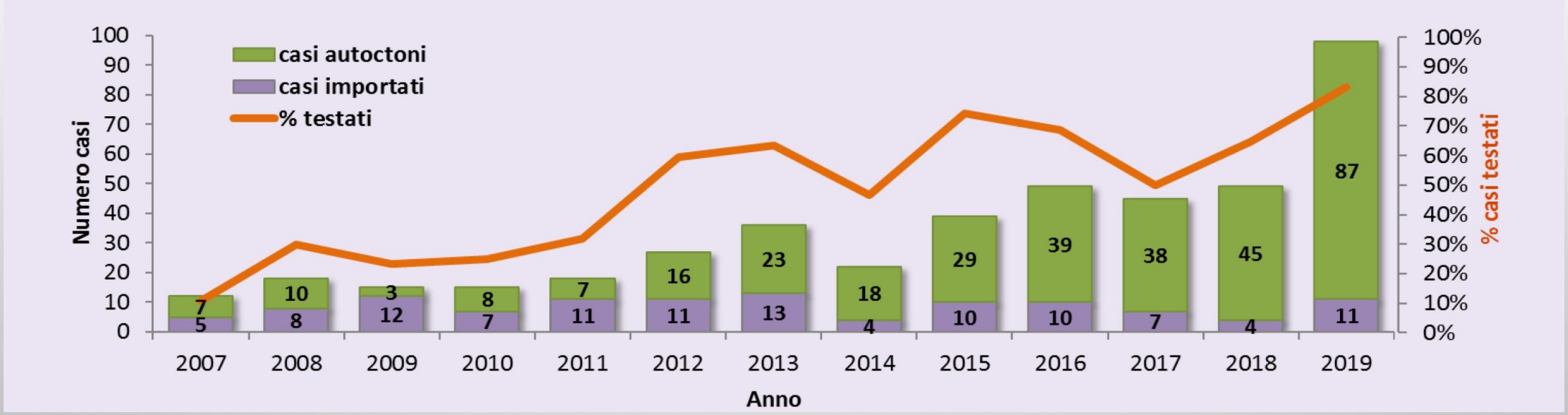


Figura 1. Prevalenza delle IgG anti-HEV per ciascuna delle 20 regioni d'Italia (2016-2017)

EPIDEMIOLOGIA
ISS

- CONSIDERANDO LE CARATTERISTICHE DEMOGRAFICHE DEI CASI DIAGNOSTICATI, IN ITALIA L'EPATITE E È PREVALENTEMENTE A CARICO DEI SOGGETTI **DI SESSO MASCHILE (80% DEI CASI) IN FASCE DI ETÀ ADULTE** (IL 55% DEI CASI HA PIÙ DI 44 ANNI) E IL **33% DEI CASI È RAPPRESENTATO DA CITTADINI STRANIERI.**
- RELATIVAMENTE AI FATTORI DI RISCHIO, IL 29% DEI SOGGETTI AFFETTI RIPORTA DI AVER COMPIUTO UN VIAGGIO IN ZONE ENDEMICHE NEI 2 MESI PRECEDENTI L'INSORGENZA DELLA MALATTIA, MENTRE IL 71% HA INVECE ACQUISITO L'INFEZIONE IN ITALIA (CASI AUTOCTONI).

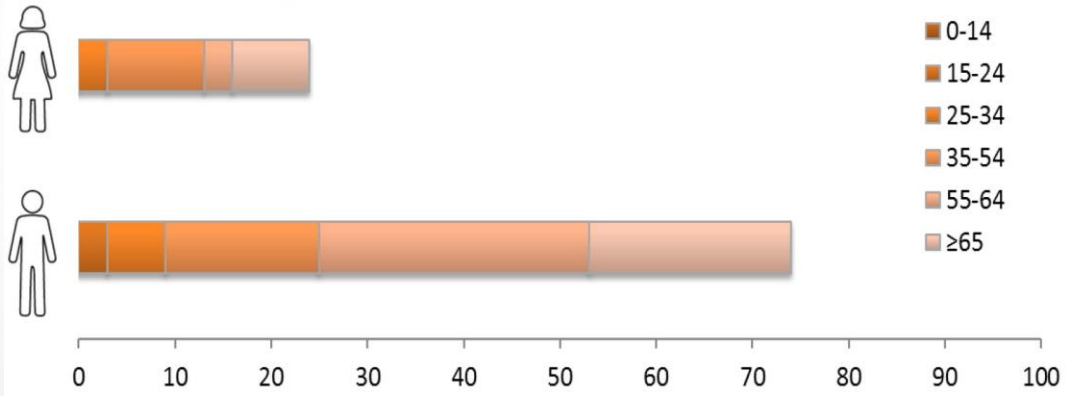
SEIEVA 2019


casi autoctoni
casi importati
% testati
Numero casi
% casi testati
Anno
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018
2019
7
5
10
8
3
12
8
7
7
11
16
11
23
13
18
4
29
10
39
10
38
7
45
4
87
11

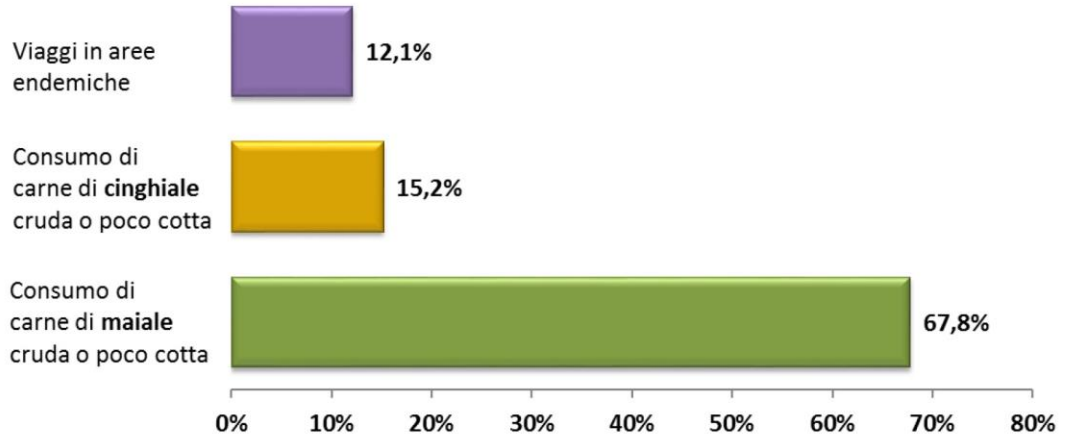
EPATITE E (2019)

Numero di casi per Regione

Numero di casi per età e sesso



Fattori di rischio



Epatite E

DATI I° SEMESTRE 2020

Numero di casi per Regione

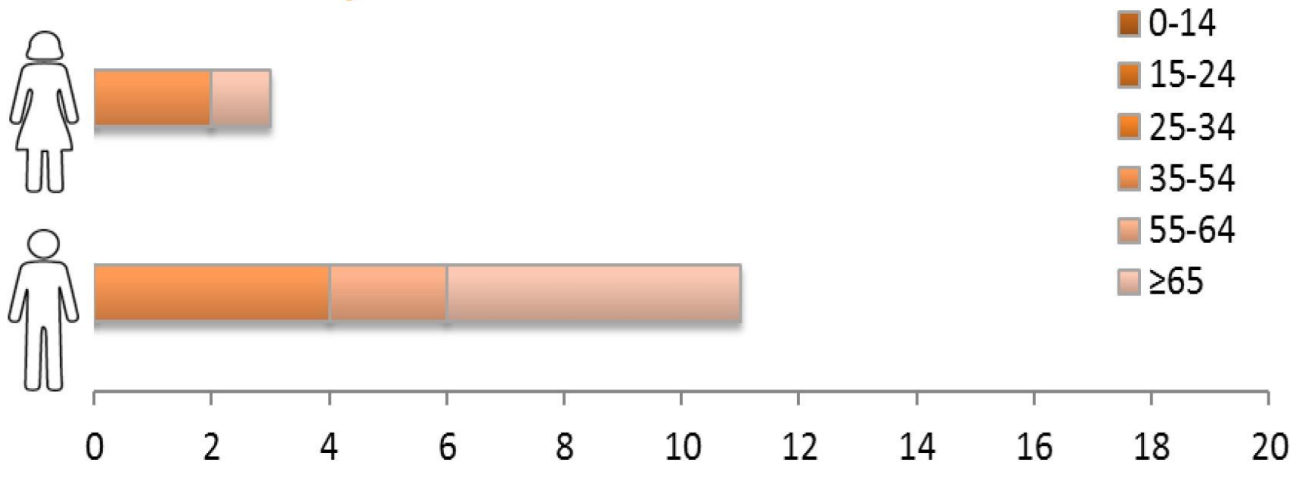
Dieci casi su 14 (71%) riportano di aver consumato insaccati di maiale, mentre 1 insaccati di cinghiale.

Il numero di nuovi casi di epatite E segnalati al SEIEVA nel primo semestre del 2020 è pari a 14.

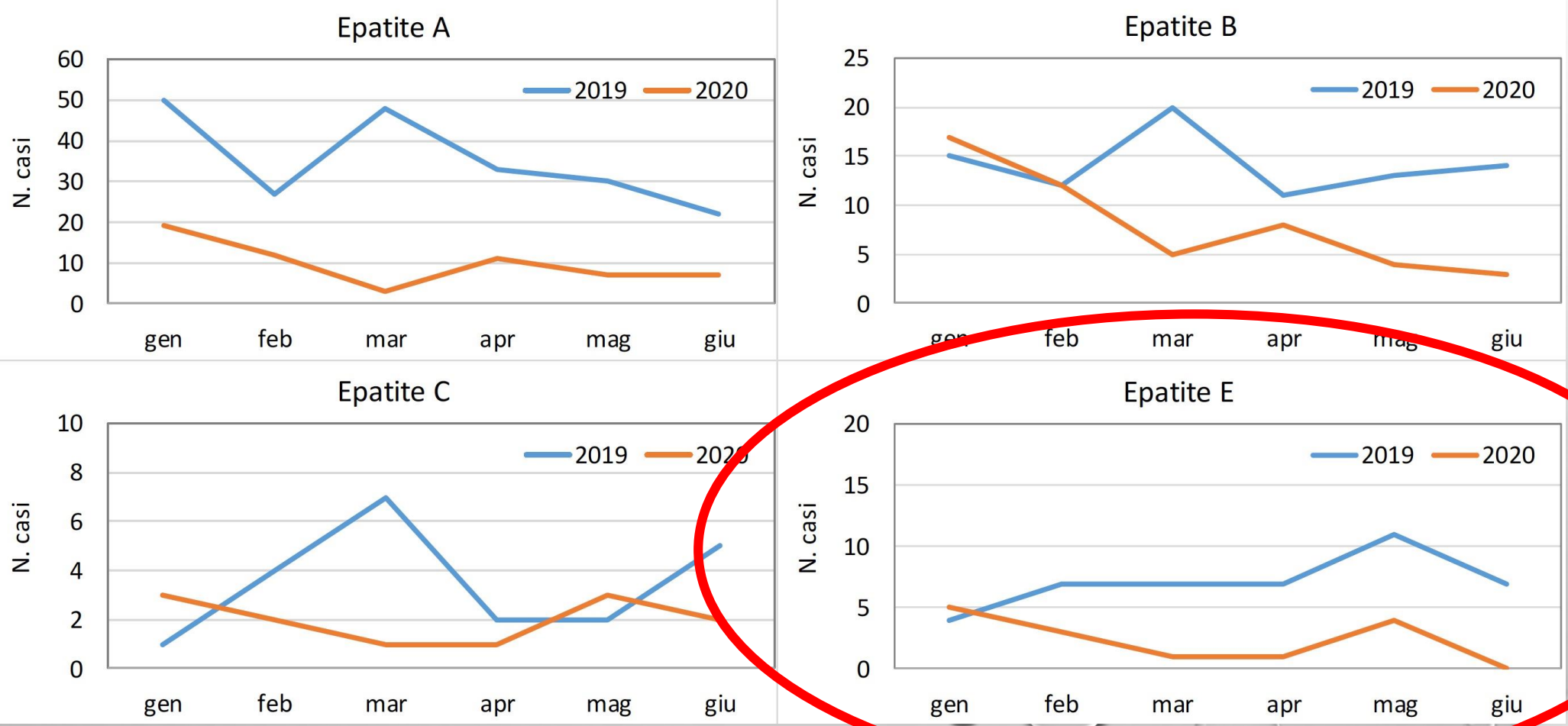
La maggioranza delle segnalazioni proviene dalle regioni Abruzzo, Toscana e Marche.

I casi sono prevalentemente di sesso maschile e tutti di età superiore a 40 anni, poco meno della metà dei casi (6) sono ultra 65-enni. Tutti i 14 casi hanno plausibilmente acquisito l'infezione in Italia in quanto non riferiscono di aver effettuato viaggi in zone endemiche.

Numero di casi per età e sesso



SEIEVA NOVEMBRE 2020

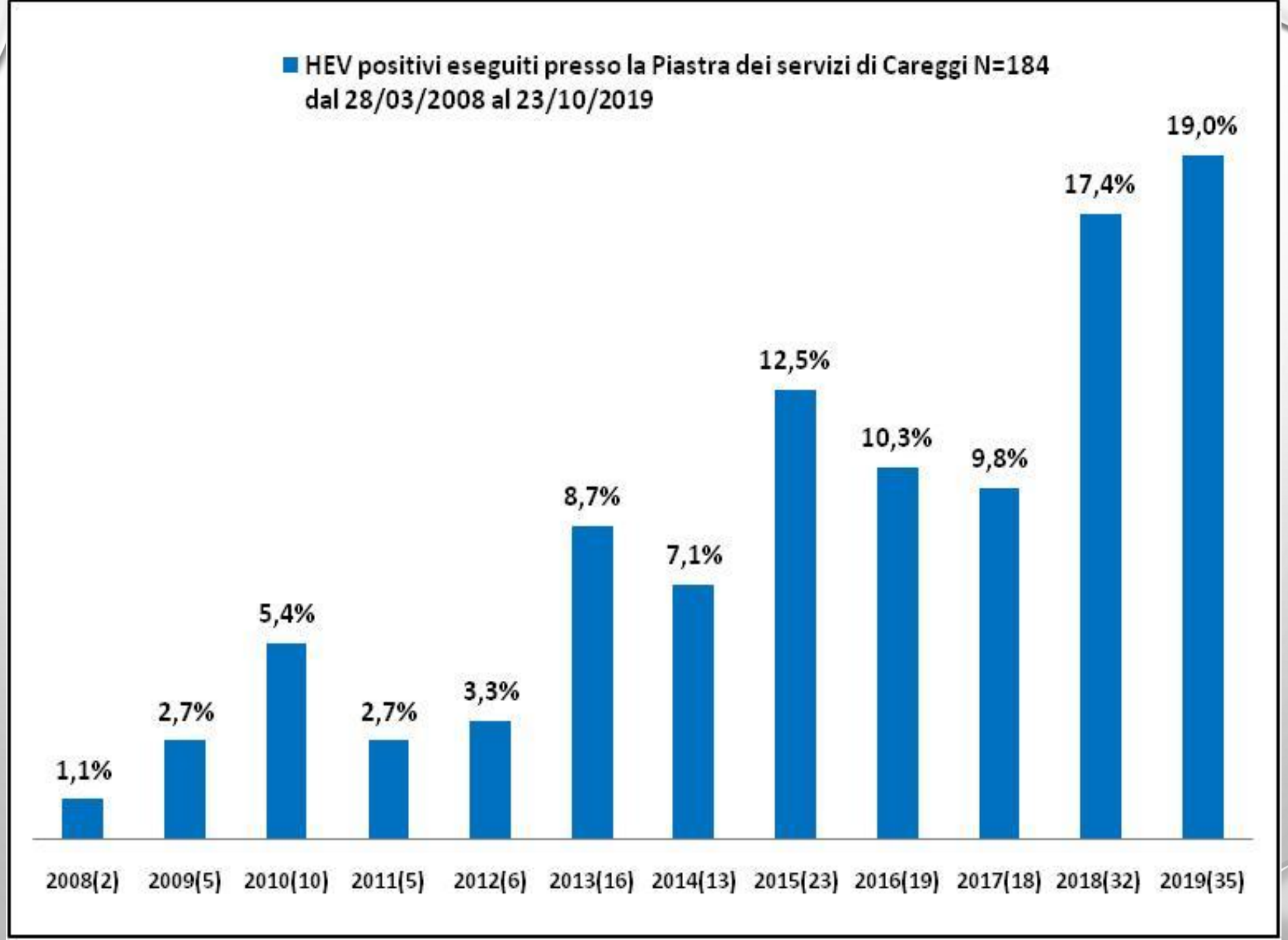


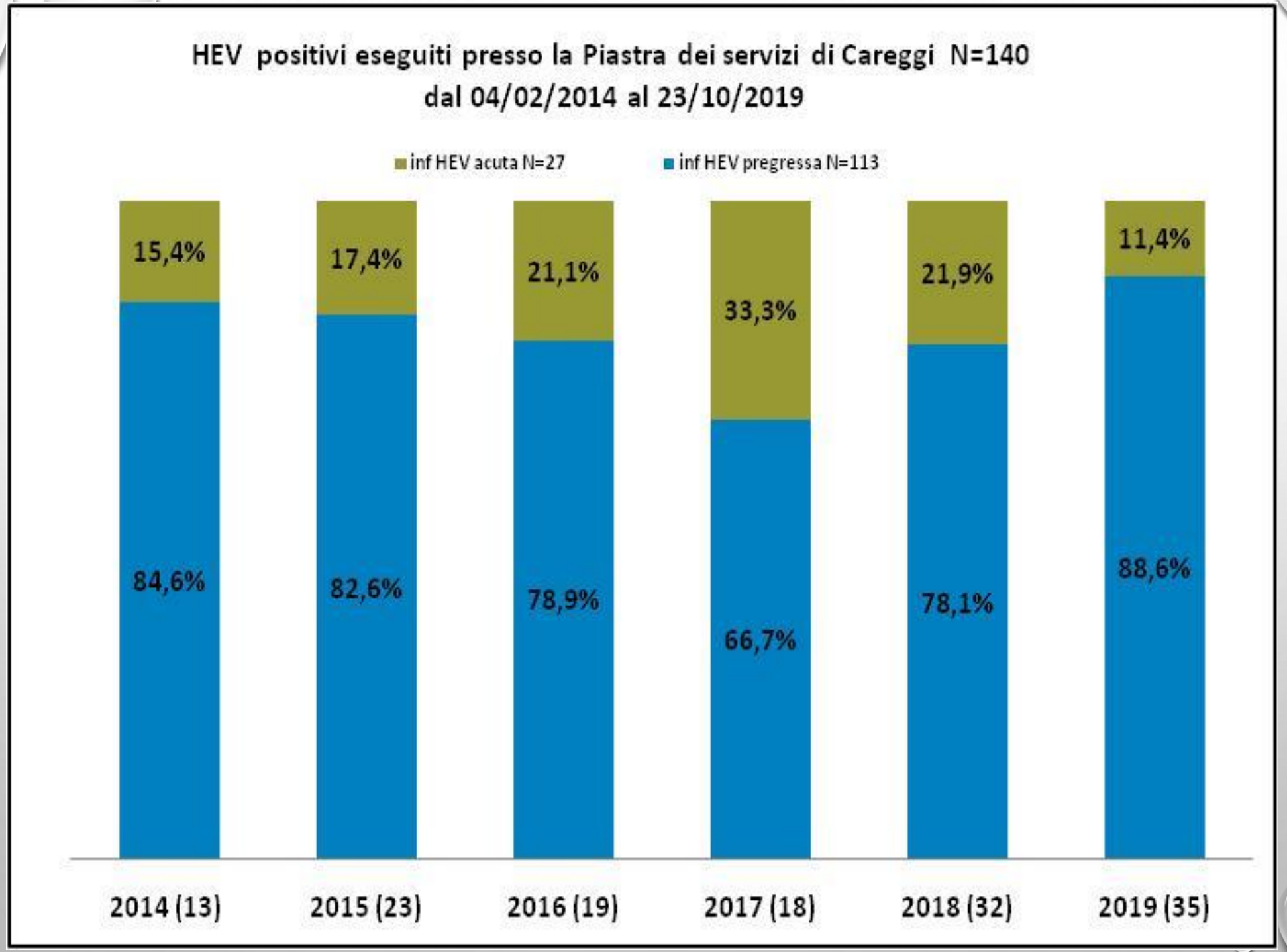
PREVALENZA HEV NEI DONATORI DI SANGUE TOSCANA

- PER QUANTO RIGUARDA LA TOSCANA SONO STATI INVIATI **623 SIERI** (LA SECONDA REGIONE ITALIANA PER NUMERO DI INVII DOPO LA SARDEGNA CHE HA INVIATO 672 SIERI) DI CUI **456 DI DONATORI MASCHI E 167 DI FEMMINE** CON UNA **PREVALENZA TOTALE DI 7,9 %** (LO STUDIO ABRUZZESE HA RILEVATO UNA PREVALENZA DEL 49%)
- I DATI DI PREVALENZA SONO DIFFERENZIATI NELLE PROVINCE:

  - **LUCCA 10.4%**
  - PRATO 9.5%
  - **FIRENZE 12.5%**
  - PISA 1.0 %
  - LIVORNO 4.2%
  - AREZZO 4.2%
  - **GROSSETO 11.5%**

- MASSA, PISTOIA E SIENA NON HANNO INVIATO DATI


HEV positivi eseguiti presso la Piastra dei servizi di Careggi N=184
dal 28/03/2008 al 23/10/2019
1,1%
2,7%
5,4%
2,7%
3,3%
8,7%
7,1%
12,5%
10,3%
9,8%
17,4%
19,0%
2008(2)
2009(5)
2010(10)
2011(5)
2012(6)
2013(16)
2014(13)
2015(23)
2016(19)
2017(18)
2018(32)
2019(35)


HEV positivi eseguiti presso la Piastra dei servizi di Careggi N=140
dal 04/02/2014 al 23/10/2019
inf HEV acuta N=27
inf HEV pregressa N=113
15,4%
17,4%
21,1%
33,3%
21,9%
11,4%
84,6%
82,6%
78,9%
66,7%
78,1%
88,6%
2014 (13)
2015 (23)
2016 (19)
2017 (18)
2018 (32)
2019 (35)

EPIDEMIOLOGIA ANIMALE/UMANA EUROPA ORIENTALE

- HEV IGG ANTIBODIES IN DOMESTIC PIGS WERE DETECTED IN 20%-54.5%, 29.2%-50%, 38.94%-50% AND 31.1%-91.7% IN SERBIA, BULGARIA, ROMANIA AND CROATIA, RESPECTIVELY. IN WILD BOARS
- SEROPREVALENCE RATES WERE UP TO 10.3%, 30.3% AND 31.1% IN ROMANIA, SLOVENIA AND CROATIA, RESPECTIVELY.

World J Gastroenterol. Jul 7, 2019; 25(25): 3168-3182

EPIDEMIOLOGIA ANIMALE
ITALIA NORD OCCIDENTALE

- WE SCREENED MOLECULARLY AND SEROLOGICALLY SERUM AND FECAL SAMPLES FROM TWO DOMESTIC AND FOUR WILD RUMINANT SPECIES COLLECTED IN VALLE D'AOSTA AND PIEMONTE REGIONS (NORTHWESTERN ITALY. HEV ANTIBODIES WERE FOUND IN SHEEP (21.6%), GOATS (11.4%), RED DEER (2.6%), ROE DEER (3.1%), AND IN ALPINE IBEX (6.3%)

Palombieri, A., Robetto, S., Di Profio, F., Sarchese, V., Fruci, P., Bona, M. C., … Di Martino, B. (2020). *Surveillance Study of Hepatitis E Virus (HEV) in Domestic and Wild Ruminants in Northwestern Italy. Animals, 10(12), 2351.*

TRASMISSIONE

- MODE OF TRANSMISSION:
  - FAECAL-ORAL (G1 AND G2)
  - ZOONOTIC (G3 AND G4)
  - BLOODBORNE, MEANING TRANSFUSION OF BLOOD/ BLOOD PRODUCTS (G3).
- INCUBATION PERIOD:
  - RANGE 15 TO 60 DAYS (AVERAGE 40 DAYS).
- IMMUNITY:
  - UNCERTAIN WHETHER INFECTION CONFERS LIFELONG IMMUNITY.
- COINCIDENTAL INFECTIONS WITHIN HOUSEHOLDS DO OCCUR, HOWEVER PERSON-TO-PERSON TRANSMISSIONS ARE RARE.

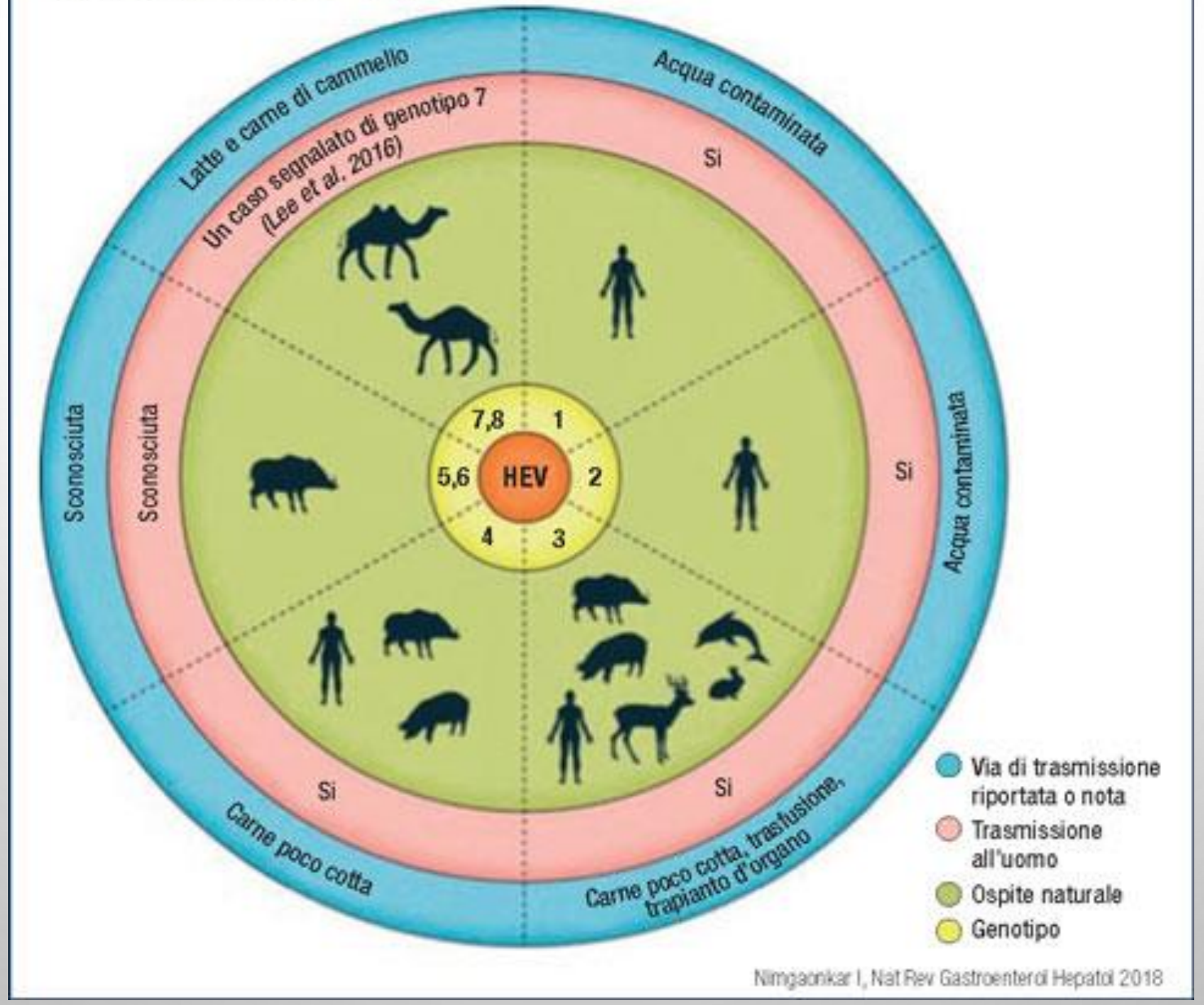
TRASMISSIONE

- IN DEVELOPING COUNTRIES THE VIRUS TRANSMITS ENTERICALLY VIA THE FAECAL-ORAL ROUTE. INFECTION IS LINKED TO THE CONSUMPTION OF HUMAN SEWAGE-CONTAMINATED FOOD OR WATER.
- IN INDUSTRIALISED COUNTRIES THE VIRUS TRANSMITS ZOONOTICALLY. THERE IS GOOD EVIDENCE FROM JAPAN AND FRANCE SUPPORTING THE ACQUISITION OF HEV THROUGH THE CONSUMPTION OF RAW/UNDERCOOKED DEER, BOAR AND PIG MEAT
- REPORTS OF TRANSFUSION TRANSMITTED HEPATITIS E DEMONSTRATE THAT THE VIRUS CAN BE ACQUIRED PARENTERALLY

TRASMISSIONE

- THE CONSUMPTION OF INFECTED MEAT IS THE MOST IMPORTANT VECTOR FOR HEV3 AND HEV4, AND THE VIRUS HAS BEEN ISOLATED FROM PORK PRODUCTS AT THE POINT OF SALE. OTHER FOOD STUFFSSUCH AS SHELLFISH AND ARABLE CROPS HAVE ALSO BEEN IMPLICATED.

Ospiti e modalità di trasmissione dei diversi genotipi di virus dell'epatite E



Nimgaonkar I, Nat Rev Gastroenterol Hepatol 2018

HEV EPIDEMIOLOGIA

- I PAESI DOVE L'INFEZIONE DA HEV SEMBRA ESSERE **MENO DIFFUSA** SONO: NUOVA ZELANDA, AUSTRALIA, CANADA, E SCOZIA (TUTTE TRA IL 4% E IL 6%).
- IN LINEA GENERALE, LA PREVALENZA DI VIREMIA TRA I DONATORI DI SANGUE NEI DIVERSI PAESI VARIA ARMONICAMENTE CON LA SIEROPREVALENZA ANTICORPALE, ATTESTANDOSI SU VALORI CHE VANNO DA 1:762 IN OLANDA A 1:9500 NEGLI STATI UNITI.

INFEZIONE ACUTA HEV

	G1/G2 (epidemica)	G3/G4 (autoctona)
Distribuzione	Paesi a basse risorse	Paesi ad alte risorse
Pattern diffusione	Sporadica ed epidemica	Sporadica
Modalità diffusione	Orofecale-alimentare	Alimentare
Forme itteriche	Frequenti	Rare (5% sintomi)
Fascia d'età più colpita	Adolescenti e giovani adulti	Adulti
Distribuzione per sesso	Paritaria	Uomini più colpiti
Manifestazioni extraepatiche	Poche	Neurologiche
Infezione cronica	Assente	Comune negli immunocompromessi

Hoofnagle et a, *NEJM*, 2012

HEV : INFEZIONE ACUTA

- IN RESOURCE-POOR SETTINGS THE MAJORITY OF CASES, BOTH SPORADIC AND EPIDEMIC, INVOLVE EITHER **HEV1 (ASIA) OR HEV2 (AFRICA AND CENTRAL AMERICA).** IN DEVELOPED COUNTRIES, LOCALLY ACQUIRED INFECTIONS ARE MOST COMMONLY CAUSED BY **HEV3, WITH HEV4 LARGELY CONFINED TO JAPAN AND CHINA.** ACUTE INFECTION IN THESE AREAS PRODUCES A WIDE VARIETY OF CLINICAL PRESENTATIONS.
- YOUNG ADULTS ARE MOST COMMONLY AFFECTED, ESPECIALLY THE 15–35 AGE GROUP, AND MEN ARE MORE LIKELY TO BE INFECTED THAN WOMEN. MOST PATIENTS EXPERIENCE AN ACUTE, SELF-LIMITING HEPATITIS. THE OVERALL MORTALITY RATE RANGES FROM 0.2% TO 4%, BUT THIS CAN BE SIGNIFICANTLY HIGHER IN AT-RISK GROUPS, SUCH AS THOSE WITH PRE-EXISTING LIVER DISEASE AND VERY YOUNG CHILDREN.
- **PREGNANT WOMEN IN DEVELOPING COUNTRIES ARE PARTICULARLY VULNERABLE, WITH MORTALITY AS HIGH AS 25%, WITH PRETERM DELIVERY IN 66% OF CASES**
- HEV-RELATED DEATHS IN PREGNANCY TYPICALLY OCCUR IN THE THIRD TRIMESTER AND ARE MOST OFTEN CAUSED BY FULMINANT HEPATIC FAILURE OR OBSTETRIC COMPLICATIONS. THE
- MECHANISMS WHICH UNDERLIE THIS EXCESS MORTALITY AND INCREASE IN PREMATURITY AND PREGNANCY LOSS ARE NOT CURRENTLY UNDERSTOOD.
- **ONLY A SMALL MINORITY OF PATIENTS, PROBABLY LESS THAN 5%, PRESENT WITH A TYPICAL PICTURE OF ACUTE VIRAL HEPATITIS**

GB Webb and HR Dalton (Therapeutic advances in Infectious Disease 2019)

HEV: INFEZIONE ACUTA

- HEV IS THE MAJOR CAUSE OF ACUTE VIRAL HEPATITIS IN SEVERAL EUROPEAN COUNTRIES; **IN FRANCE, GERMANY AND THE UK DURING 2014 AND 2015, THERE WERE MORE REPORTED CASES OF ACUTE HEPATITIS E THAN HEPATITIS A OR ACUTE HEPATITIS B.**
- OLDER MEN ARE PREDOMINANTLY AFFECTED, WITH **A MALE TO FEMALE RATIO OF AROUND 3:1 AND A MEDIAN AGE AROUND 63 YEARS.** IT IS THOUGHT THAT THIS IS DUE TO HOST FACTORS RATHER THAN ANY DIFFERENCE IN EXPOSURE, WITH PRE-EXISTING SUBCLINICAL LIVER DISEASE SUGGESTED AS A POSSIBLE RISK FACTOR. AN ENGLISH STUDY FOUND AN OVERREPRESENTATION OF EXCESS ALCOHOL CONSUMPTION AND DIABETES AMONGST INDIVIDUALS WITH ACUTE HEPATITIS E, BOTH OF WHICH ARE RISK FACTORS FOR HEPATIC FIBROSIS AND STEATOSIS.
- **PROGRESSION TO ACUTE LIVER FAILURE IS RARE, BUT A SMALL NUMBER OF INDIVIDUAL CASES HAVE BEEN REPORTED IN EUROPE, AND A SINGLE-CENTRE GERMAN STUDY OF 80 PATIENTS WITH ACUTE LIVER FAILURE FOUND THAT HEV WAS THE MOST LIKELY CAUSE IN AROUND 10% OF CASES.**

GB Webb and HR Dalton (Therapeutic advances in Infectious Disease 2019)

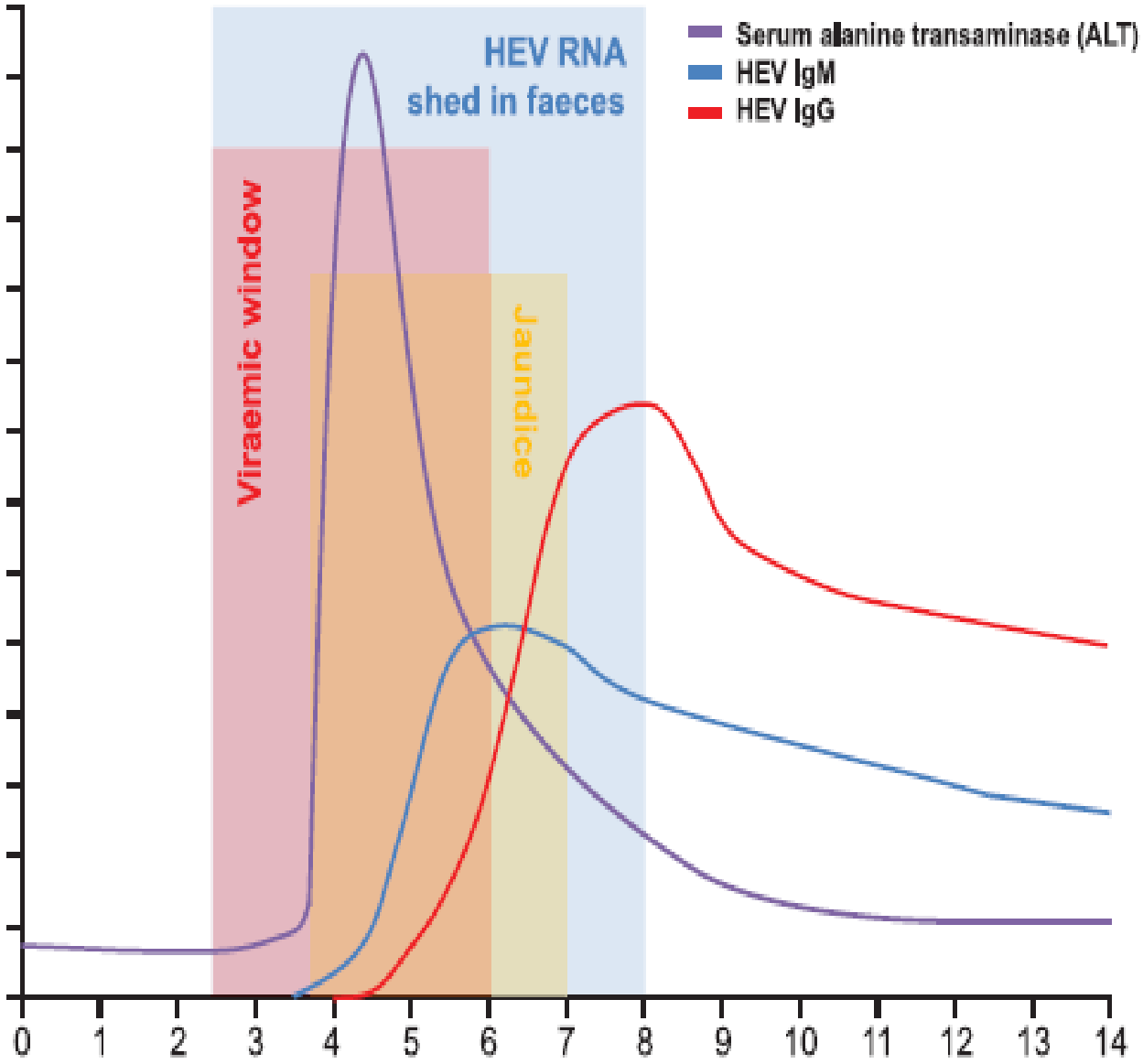


Figure 1. HEV viral detection in blood and stool: serological and biochemical response to acute HEV infection over time. ALT, alanine transaminase; HEV, hepatitis E virus.

HEV : INFEZIONE CRONICA

- CHRONIC HEV INFECTION CAN OCCUR IN IMMUNOSUPPRESSED INDIVIDUALS, INCLUDING TRANSPLANT RECIPIENTS, HIV-POSITIVE PATIENTS AND PATIENTS RECEIVING CHEMOTHERAPY FOR HAEMATOLOGICAL MALIGNANCIES.
- ALL CASES REPORTED TO DATE HAVE INVOLVED HEV3 OR HEV4. THE BULK OF THE LITERATURE ON CHRONIC HEV INFECTION CONCERNS SOLID-ORGAN TRANSPLANT RECIPIENTS, BUT THE CLINICAL PRESENTATION IS SIMILAR IN OTHER IMMUNOCOMPROMISED COHORTS. THE MAJORITY OF CASES ARE ASYMPTOMATIC, WITH PERSISTENT MILD TO MODERATE DERANGEMENT OF LIVER FUNCTION TESTS (LFTS). A PROPORTION OF PATIENTS HAVE NORMAL OR NEAR-NORMAL LIVER ENZYME LEVELS, AND SOME REMAIN ANTI-HEV IGG AND IGM NEGATIVE DESPITE THE PRESENCE OF PERSISTENT VIRAL REPLICATION.

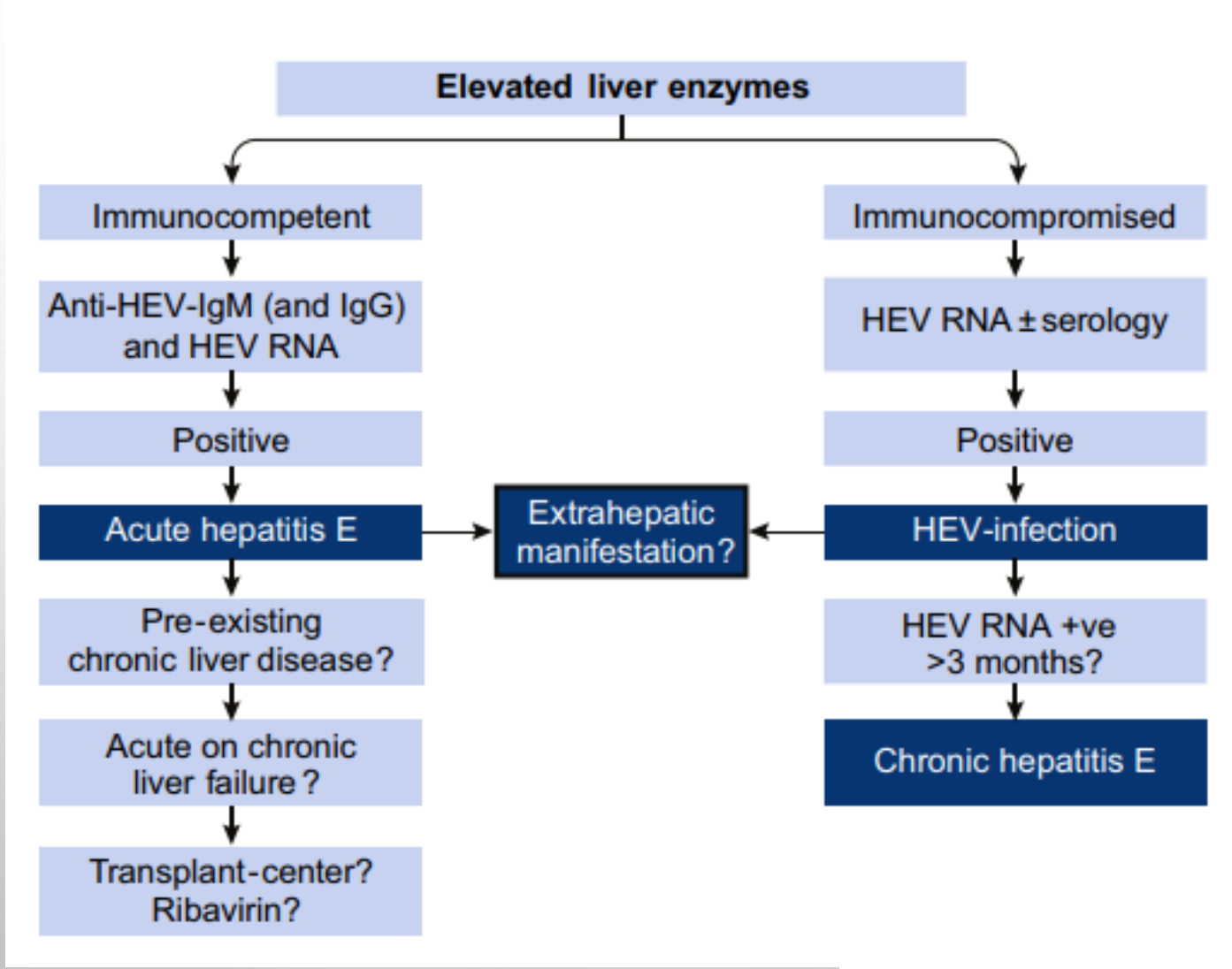
GB Webb and HR Dalton (Therapeutic advances in Infectious Disease 2019)

HEV : INFEZIONE CRONICA

- IN HIV POSITIVE PATIENTS, CHRONIC CO-INFECTION IS UNCOMMON, AND SEEN ONLY IN INDIVIDUALS WITH A VERY LOW CD4+COUNT (< 200 CELLS/MM^3).
- FACTORS PREDICTIVE OF CHRONIC INFECTION IN OTHER IMMUNOSUPPRESSED GROUPS ARE YET TO BE IDENTIFIED.

GB Webb and HR Dalton (Therapeutic advances in Infectious Disease 2019)

ALGORITMO DIAGNOSTICO



EASL Clinical Practice Guidelines on hepatitis E virus infection☆

European Association for the Study of the Liver*

HEV AND NEUROLOGICAL INJURY

- A THIRD CASE-CONTROL STUDY, CONDUCTED IN JAPAN, FOUND THAT 4.8% OF 63 PATIENTS WITH GBS WERE ANTI-HEV IGM POSITIVE DURING THE ACUTE PHASE OF THEIR ILLNESS.
- MORE RECENTLY, A BELGIAN COHORT STUDY FOUND THAT 8% OF PATIENTS WITH GBS HAD EVIDENCE OF HEV INFECTION. THE CLINICAL PICTURE OF HEV-ASSOCIATED GBS IS INDISTINGUISHABLE FROM CASES NOT ASSOCIATED WITH HEV.
- NA (NEURALGIC AMYOTROPHYC) ALSO KNOWN AS BRACHIAL NEURITIS OR PARSONAGE– TURNER SYNDROME, IS AN ACUTE MONOPHASIC NEUROLOGICAL INJURY AFFECTING THE BRACHIAL PLEXUS. THE AETIOLOGY OF THIS CONDITION IS NOT FULLY UNDERSTOOD, BUT IN COMMON WITH GBS IT IS THOUGHT TO HAVE A POSTINFECTIOUS, IMMUNE-MEDIATED COMPONENT.
- A TOTAL OF 12 CASES OF HEV-ASSOCIATED ENCEPHALITIS/MYELITIS HAVE BEEN DESCRIBED IN INDIVIDUAL REPORTS AND SMALL CASE SERIES. SEVEN WERE FROM EUROPE, FOUR WERE FROM ASIA AND ONE WAS FROM THE USA.

HEV AND RENAL INJURY

- HEV-ASSOCIATED GLOMERULAR DISEASE HAS BEEN REPORTED IN BOTH IMMUNOCOMPETENT AND IMMUNOSUPPRESSED PATIENTS. ALL BUT ONE CASE HAVE INVOLVED HEV3.
- A FRENCH STUDY EXAMINED RENAL FUNCTION AND HISTOLOGY IN A COHORT OF SOLID-ORGAN TRANSPLANT RECIPIENTS INFECTED WITH HEV. RENAL FUNCTION WAS SIGNIFICANTLY IMPAIRED IN BOTH THE ACUTE AND CHRONIC PHASES OF INFECTION. RENAL BIOPSIES WERE PERFORMED ON PATIENTS WITH CONCOMITANTLY INCREASED PROTEINURIA, AND THESE SHOWED FEATURES OF MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS, IGA NEPHROPATHY AND NEPHROANGIOSCLEROSIS.
- MOST PATIENTS ALSO HAD CRYOGLOBULINAEMIA. THESE EFFECTS ALL APPEAR TO BE RELATED TO HEV INFECTION.
- OTHER CAUSES OF RENAL IMPAIRMENT WERE EXCLUDED AND VIRAL CLEARANCE RESULTED IN IMPROVED ESTIMATED GLOMERULAR FILTRATION RATE, REDUCED PROTEINURIA AND RESOLUTION OF CRYOGLOBULINAEMIA.

HEV AND HAEMATOLOGICAL DISORDERS

- THROMBOCYTOPAENIA HAS BEEN REPORTED IN THE CONTEXT OF BOTH HEV1 AND HEV3 INFECTION. A UK STUDY FOUND THAT 12/106 PATIENTS INFECTED WITH HEV PRESENTED WITH A LOW PLATELET COUNT. ONLY THREE OF THESE PATIENTS HAVE PLATELET COUNTS BELOW 100 $\times 10^9$/L, AND THERE WERE NO SIGNIFICANT CLINICAL CONSEQUENCES. NINE CASES OF MORE SEVERE THROMBOCYTOPAENIA HAVE BEEN REPORTED, WITH A MEDIAN PLATELET COUNT OF 10×10^9/L.
- ALL OF THESE PATIENTS HAD ELEVATED ALT LEVELS (MEDIAN: 1045 IU/L)
- A NUMBER OF OTHER HAEMATOLOGICAL CONDITIONS HAVE BEEN REPORTED IN ASSOCIATION WITH HEV INFECTION, MOSTLY AS SINGLE CASE REPORTS. THIS INCLUDES AUTOIMMUNE HAEMOLYTIC ANAEMIA, APLASTIC ANAEMIA AND PURE RED-CELL APLASIA.

Extrahepatic manifestations

Organ system	Clinical syndrome	Notes
Neurological	• Neuralgic amyotrophy* • Guillain–Barré syndrome* • Meningoencephalitis* • Mononeuritis multiplex • Myositis • Bell's palsy, vestibular neuritis, and peripheral neuropathy	• ~150 cases of neurological injury (in HEV GT 3); mainly Europe • Most (>90%) cases in the immunocompetent
Renal*	• Membranoproliferative and membranous glomerulonephritis • IgA nephropathy	• Mainly immunosuppressed GT 3-infected patients • Renal function improves and proteinuria levels decrease following HEV clearance
Haematological	• Thrombocytopenia • Monoclonal immunoglobulin • Cryoglobulinaemia • Aplastic anaemia† • Haemolytic anaemia†	• Mild thrombocytopenia is common; occasionally severe • Reported in 25% of cases of acute HEV in UK study • Occurs mainly in association with renal disease
Other	• Acute pancreatitis • Arthritis† • Myocarditis† • Autoimmune thyroiditis†	• 55 cases worldwide. HEV GT 1 only; usually mild

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Table 5. Suggested testing for HEV.

Immunological status	Patients who should be tested for HEV
Immunocompetent	• Any patient with biochemical evidence of hepatitis • Suspected drug-induced liver injury • Decompensated chronic liver disease* • Neuralgic amyotrophy* • Guillain-Barré syndrome* • Encephalitis* • Patients with unexplained acute neurology and a raised ALT**
Immunocompromised (developed countries)	• As above • Persistently abnormal ALT***

* Testing should be done at disease onset, irrespective of ALT results.
** Testing should be done at disease onset, if ALT is abnormal.
*** If the ALT is above the limit of normal on more than one occasion. ALT, alanine aminotransferase; HEV, hepatitis E virus.

Laboratory diagnosis of HEV infection

- Acute HEV infection can be diagnosed by detection of anti-HEV antibodies
  - IgM, IgG or both by enzyme immunoassays in combination with HEV NAT
- Serological testing relies upon detection of anti-IgM and (rising) IgG

Infection status	Positive markers
Current infection – acute	• HEV RNA • HEV RNA + anti-HEV IgM • HEV RNA + anti-HEV IgG* • HEV RNA + anti-HEV IgM + anti-HEV IgG • Anti-HEV IgM + anti-HEV IgG (rising) • HEV antigen
Current infection – chronic	• HEV RNA (± anti-HEV) ≥3 months • HEV antigen
Past infection	• Anti-HEV IgG

*Patients with re-infection are typically anti-HEV IgM negative, but IgG and PCR positive

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Molecular analysis of HEV

- Detection of HEV RNA in blood or stool is indicative of HEV infection
- In immunosuppressed patients with chronic HEV, anti-HEV antibodies are often undetectable
  - NATs are the only reliable means of diagnosis
- In chronic cases, viral load testing should be used
  - To evaluate patient response to treatment
  - To identify relapsing infections

Recommendations	Grade of evidence	Grade of recommendation
• **A combination of serology and NAT testing** should be used to diagnose HEV infection	A	1
• NAT testing should be used to diagnose chronic HEV infection	A	1

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TRATTAMENTO
INFEZIONE ACUTA

- NELLA MAGGIOR PARTE DEI CASI NON NECESSARIO ALCUN TRATTAMENTO
- TRATTAMENTO DELL'INSUFFICIENZA EPATICA
- SEGNALAZIONI DI TRATTAMENTI CON RIBAVIRINA
  - MIGLIORAMENTO DEGLI INDICI DI CITOLISI
  - CLEARANCE VIRALE
  - .. MA MANCANZA DI GRUPPI DI CONTROLLO E STUDI ETEROGENEI NEI REGIMI UTILIZZATI

TRATTAMENTO
INFEZIONE CRONICA

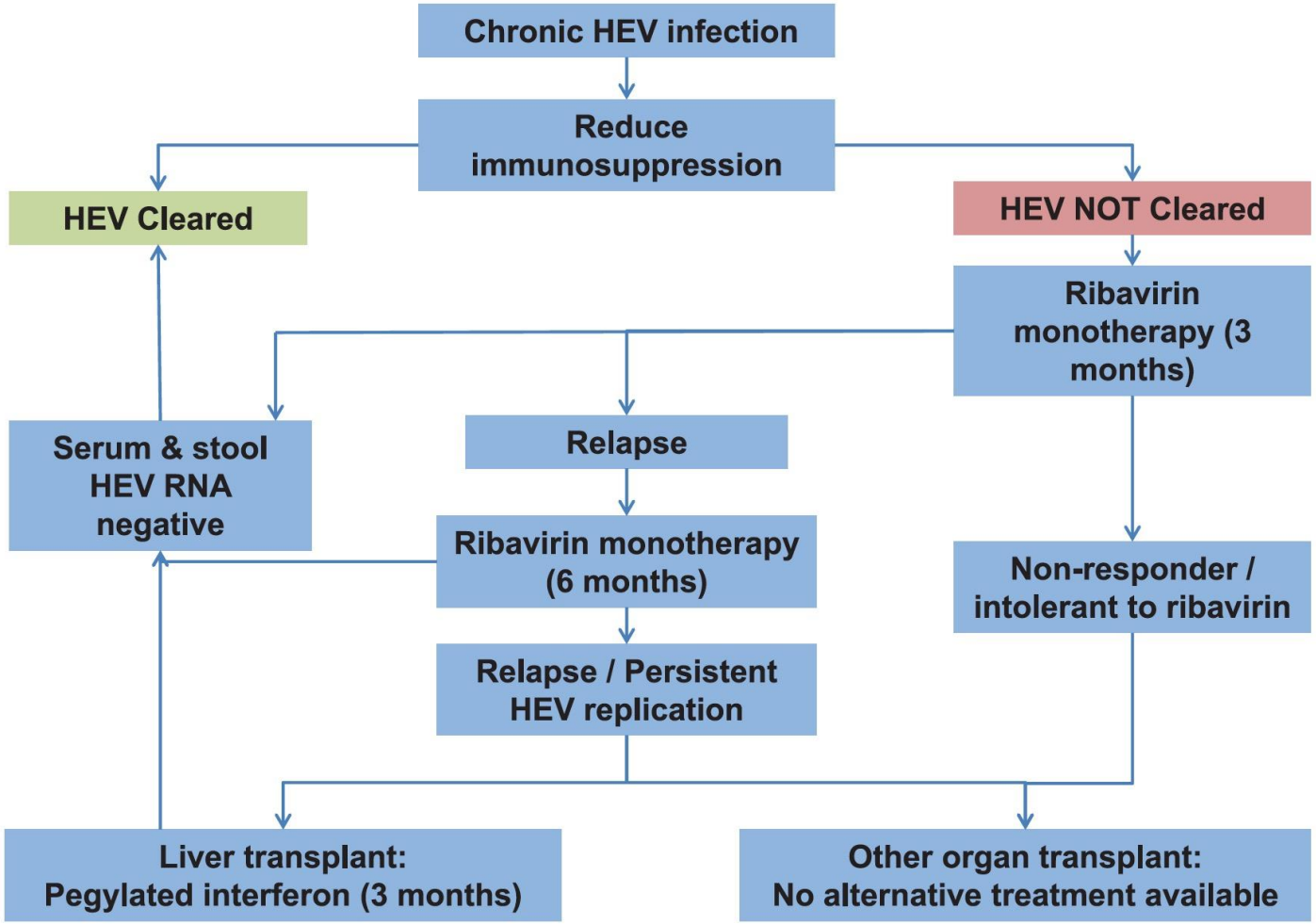

Figure 2. Treatment algorithm for chronic HEV infection in solid-organ transplant recipients (adapted from Dalton, et al.[8]) HEV, hepatitis E virus.

Management of HEV infection

- Optimal treatment duration in patients who test HEV RNA positive after 4 or 8 weeks of therapy and who are HEV RNA negative after 12 weeks of therapy is unknown*
- Optimal therapeutic approach unknown in patients who show no response to ribavirin and/or who relapse after retreatment*

Recommendation	Grade of evidence	Grade of recommendation
• If HEV RNA is still detectable in serum and/or stool after 12 weeks, ribavirin monotherapy may be continued for an additional 3 months (6 months therapy overall)	C	2
• Liver transplant recipients who show no response to ribavirin can be considered for treatment with pegylated interferon-α	C	2

*Grade of evidence C

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Prevention of HEV infection

- Consumption of undercooked meat from pigs, wild boar, and deer is a clear risk factor for HEV infection in Europe
  - *In vitro* food preparation data inconclusive
- Risk of patient-to-patient transmission is poorly defined
  - Sexual transmission has been described in MSM
  - Stool contains high amounts of infectious HEV particles
    - Strict hygiene is required
- A vaccine has been developed but is only licensed in China

Recommendations	Grade of evidence	Grade of recommendation
• Immunocompromised individuals and those with chronic liver diseases should avoid consumption of undercooked meat (pork, wild boar and venison) and shellfish	B	1
• Suggested that immunocompromised patients consume meat only if it has been thoroughly cooked to ≥70°C	B	2

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HEV - VACCINI

- SONO AL MOMENTO IN SVILUPPO DUE VACCINI RICOMBINANTI CONTRO L'HEV, UNO DI GLAXOSMITHKLINE, L'ALTRO DI XIAMEN INNOVAX BIOTECH (NOME COMMERCIALE HECOLIN); ENTRAMBI SONO STATI OGGETTO DI *TRIAL* CLINICI DI BREVE DURATA PER VALUTARNE L'EFFICACIA.

- HECOLIN È INVECE SUL MERCATO CINESE DAL 2012, MA FINORA NESSUN *TRIAL* NE AVEVA VALUTATO L'EFFICACIA SU VASTE POPOLAZIONI E A LUNGO TERMINE.

- RECENTEMENTE LO STUDIO PUBBLICATO SUL *NEW ENGLAND*, FINANZIATO TRA L'ALTRO DAL MINISTERO CINESE PER LA SCIENZA E LA TECNOLOGIA, NE HA DECRETATO L'EFFICACIA SU UN PERIODO DI ALMENO 4 - 5 ANNI (TRE SOMMINISTRAZIONI 0, 1 E 6 MESI). PROTEZIONE 87% A 4 ANNI,EFFICACIA SOLO NEL GENOTIPO 4

CIAONE !!!

Grazie per l'attenzione