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COMMISSION STAFF WORKING DOCUMENT

Comprehensive 2025 Health Threat Prioritisation Assessment for medical countermeasures

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ABBREVIATIONS AND ACRONYMS

Abbreviation	Full term
4CMenB	Multicomponent meningococcal serogroup B vaccine (Bexsero)
AFM	Acute flaccid myelitis
AFP	Acute flaccid paralysis
AI	Artificial intelligence
AIDS	Acquired immunodeficiency syndrome
AMR	Antimicrobial resistance
API	Active pharmaceutical ingredient
AST	Antimicrobial susceptibility testing
ATM-AVI	Aztreonam–avibactam
AWaRe	Access, Watch and Reserve (WHO antibiotic classification)
BDBV	Bundibugyo ebolavirus
BLI	β-lactamase inhibitor
BPPL	Bacterial Priority Pathogens List (WHO)
BPaL / BPaLM	Bedaquiline–pretomanid–linezolid (± moxifloxacin) regimen
BSI	Bloodstream infection
BSL	Biosafety level
C3GRE	Third-generation cephalosporin-resistant Enterobacterales
CBRN	Chemical, biological, radiological and nuclear
CDC	Centers for Disease Control and Prevention (United States)
CEPI	Coalition for Epidemic Preparedness Innovations
CFR	Case fatality rate
CHIK / CHIKV	Chikungunya (virus)
COVID-19	Coronavirus disease 2019
CRAB	Carbapenem-resistant *Acinetobacter baumannii*
CRE	Carbapenem-resistant Enterobacterales
CRP	C-reactive protein
CRPA	Carbapenem-resistant *Pseudomonas aeruginosa*
CSF	Cerebrospinal fluid
cUTI	Complicated urinary tract infection
CVV	Candidate vaccine virus
DALY	Disability-adjusted life year
DNA	Deoxyribonucleic acid
DOBV	Dobrava–Belgrade orthohantavirus
DRC	Democratic Republic of the Congo
EAGLE-1	Evaluation of gepotidacin against standard therapy (Phase 3 trial)
EARS-Net	European Antimicrobial Resistance Surveillance Network
EBOV	Ebola virus (*Zaire ebolavirus*)
ECDC	European Centre for Disease Prevention and Control
EEE / EEEV	Eastern equine encephalitis (virus)
EFSA	European Food Safety Authority
EMA	European Medicines Agency
ENPEN	European Non-Polio Enterovirus Network
EPAR	European Public Assessment Report
ESAC-Net	European Surveillance of Antimicrobial Consumption Network
EU	European Union
EU/EEA	European Union / European Economic Area
EURGen-Net	European Antimicrobial Resistance Genes Surveillance Network
EVD	Ebola virus disease
EV-A71	Enterovirus A71
EV-D68	Enterovirus D68
FDA	Food and Drug Administration (United States)

Abbreviation	Full term
FPPL	Fungal Priority Pathogens List (WHO)
G7	Group of Seven
GARDP	Global Antibiotic Research and Development Partnership
gbMSM	Gay, bisexual and other men who have sex with men
GLASS	Global Antimicrobial Resistance and Use Surveillance System
GLASS-FUNGI	GLASS module for invasive fungal infections
GMMA	Generalized Modules for Membrane Antigens
HAI	Healthcare-associated infection
HAI-Net	Healthcare-Associated Infections Surveillance Network
HCPS	Hantavirus cardiopulmonary syndrome
HERA	Health Emergency Preparedness and Response Authority
HFMD	Hand, foot and mouth disease
HFRS	Haemorrhagic fever with renal syndrome
HIV	Human immunodeficiency virus
HPAI	Highly pathogenic avian influenza
HTNV	Hantaan orthohantavirus
ICTV	International Committee on Taxonomy of Viruses
IDV	Influenza D virus
IIV	Inactivated influenza vaccine
IL	Interleukin
IND	Investigational New Drug
IPC	Infection prevention and control
IPV	Inactivated poliovirus vaccine
JEV	Japanese encephalitis virus
JIACRA	Joint Interagency Antimicrobial Consumption and Resistance Analysis
JRC	Joint Research Centre
JUNV	Junín mammarenavirus
LAIV	Live-attenuated influenza vaccine
LASV	Lassa mammarenavirus
LMICs	Low- and middle-income countries
LUJV	Lujo mammarenavirus
MAH	Marketing authorisation holder
MAPS	Multiple Antigen Presenting System
MARV	Marburg virus
MBL	Metallo-β-lactamase
MCDA	Multicriteria decision analysis
MCM	Medical countermeasure(s)
MDR	Multidrug-resistant
MenB	Meningococcal serogroup B
MERS-CoV	Middle East respiratory syndrome coronavirus
MRSA	Methicillin-resistant *Staphylococcus aureus*
MPXV	Mpox virus
MVD	Marburg virus disease
NDM / NDM-5	New Delhi metallo-β-lactamase
NIAID	National Institute of Allergy and Infectious Diseases
nOPV	Novel oral poliovirus vaccine
OPV	Oral poliovirus vaccine
ORF	Open reading frame
PADO	Paediatric Drug Optimization
PCR	Polymerase chain reaction
PCT	Procalcitonin
PEP	Post-exposure prophylaxis
PHEIC	Public health emergency of international concern

Abbreviation	Full term
PPE	Personal protective equipment
PRAC	Pharmacovigilance Risk Assessment Committee
PrEP	Pre-exposure prophylaxis
PUUV	Puumala orthohantavirus
R&D	Research and development
R_0	Basic reproduction number
RG	Risk group
RNA	Ribonucleic acid
RR-TB	Rifampicin-resistant tuberculosis
RSV	Respiratory syncytial virus
RT-PCR	Reverse transcription polymerase chain reaction
RVF / RVFV	Rift Valley fever (virus)
SEOV	Seoul orthohantavirus
SFTS / SFTSV	Severe fever with thrombocytopenia syndrome (virus)
SIOV	Sin Nombre orthohantavirus
SoHO	Substances of human origin
ST / ST39	Sequence type
TB	Tuberculosis
TAFV	Taï Forest ebolavirus
TBE / TBEV	Tick-borne encephalitis (virus)
TC-83	Live-attenuated VEEV vaccine strain
TESSy	The European Surveillance System
TRL	Technology readiness level
uUTI	Uncomplicated urinary tract infection
VEE / VEEV	Venezuelan equine encephalitis (virus)
VREfm	Vancomycin-resistant *Enterococcus faecium*
VSV	Vesicular stomatitis virus
WEE / WEEV	Western equine encephalitis (virus)
WHO	World Health Organization
WGS	Whole-genome sequencing
WNV	West Nile virus
XDR	Extensively drug-resistant
YFV	Yellow fever virus
ZIKV	Zika virus

GENERAL INTRODUCTION

The objective of the Comprehensive 2025 Health Threat Prioritisation Assessment for medical countermeasures ('comprehensive assessment') is to provide information on the Commission's measures to improve preparedness and response to serious cross-border threats in the area of medical countermeasures (MCM) ([1]). In particular, it aims to identify the priority threats that require interventions to address vulnerabilities and strategic dependencies related to the development, production, procurement, stockpiling and distribution of MCM.

The document has been drafted in accordance with the MCM strategy published on 9 July 2025 ([2]). This provides that the Commission will, together with EU Member States, continuously review and update the list of priority health threats that require MCM.

Based on prioritisation exercises performed at EU and global level, as well as further considerations specific to the mandate of the European Commission's Directorate-General 'Health Emergency Preparedness and Response Authority' (HERA), this Comprehensive Assessment lists the pathogens or agents that have the potential to cause a public health emergency at EU level and therefore are the most obvious candidates for EU interventions in the area of MCM. The Comprehensive Assessment not only considers the likelihood of these threats materialising and their potential impact on health, but also assesses the adequacy of the current MCM portfolio to respond to these threats, focusing on availability of vaccines and therapeutics.

The Comprehensive 2025 Health Threat Prioritisation Assessment for medical countermeasures provides a useful starting point for EU-level interventions in the area of MCM development, production, procurement, stockpiling and distribution. It lays the foundation for guiding the EU's efforts to strengthen the EU's preparedness and response in the area of MCM – e.g. to guide decision-making on MCM relevant for stockpiling under rescEU –, but does not prescribe specific investments or operational decisions.

This present document identifies threats that have the potential to cause a public health emergency at EU level, but it also considers the global burden of health threats and their potential to cause the WHO to declare a public health emergency of international concern (PHEIC), which may also warrant EU support, where this is consistent with the EU's strategic objectives and international solidarity commitment.

It underpins the implementation of the MCM Strategy and is intended to play a dual role: both as an internal working document to guide EU-level preparedness and response

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([1]) As per Article 3, point (10), of Regulation (EU) 2022/2371, 'medical countermeasures' means medicinal products for human use as defined in Directive 2001/83/EC of the European Parliament and of the Council (27), medical devices as defined in point 12 of this Article and other goods or services that are necessary for the purpose of preparedness for and response to serious cross-border threats to health. For the purpose of this exercise, countermeasures against radiological and nuclear threats are also covered for the purpose of this Staff Working Document.

([2]) COM(2025) 529 final. Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions: Preparing the EU for the next health crisis : a Medical Countermeasures Strategy https://health.ec.europa.eu/document/download/1be3e462-bd50-4c64-b147-add9d1d5a580_en?filename=com_2025-529-1_act_en.pdf.

planning, as well as a reference for external audiences, including Member States, EU institutions, and, importantly, scientific community and industry.

This Staff Working Document has been developed in close collaboration with Commission Services, and takes into consideration input received from Member States through the HERA Board in May 2025, and November 2025.

The Comprehensive Assessment builds on four major threat categories:

1. **respiratory or contact-based viruses with pandemic potential**: highly transmissible viruses with a history or likelihood of causing large-scale outbreaks and influenced by, for example, biodiversity loss;

2. **vector-borne or animal-reservoir viruses with epidemic potential**: viruses whose spread is accelerated by climate change and other environmental factors, which are qualified as a specific threat category due to their growing relevance for the Europe (the fastest warming continent according to the European Environment Agency);

3. **armed conflict-related threats** and **chemical, biological, radiological and nuclear (CBRN) threats**;

4. **antimicrobial resistance (AMR)**: a rising global concern that threatens the efficacy of existing treatments and increases the burden of infectious diseases.

All four major threat categories are distinct and separate from each other. However, the underlying pathogens for the first two threat categories are closely linked and these two threat categories are therefore treated jointly in this Report.

In accordance with a recommendation by HERA's Advisory Forum, climate-related factors receive more prominent attention, specifically the first three of the four threat categories (viral families with epidemic and pandemic potential, and AMR).

Chapter I (viral families with epidemic and pandemic potential) focuses on the 12 viral families of concern. These include 11 RNA viral families and 1 DNA viral family (*Poxviridae*), which all have the potential to cause significant outbreaks or pandemics. The chapter summarises the following five points for each priority viral family: (i) their potential to cause a PHEIC according to the World Health Organization (WHO); (ii) the current epidemiological situation (including, when available, the risk assessments delivered by the European Centre for Disease Prevention and Control (ECDC)); (iii) their potential to cause public health emergencies in the EU; (iv) the current availability of vaccines and therapeutics; and (v) the impact of climate change and biodiversity loss.

Chapter II (armed conflict-related and chemical, biological, radiological and nuclear threats) focuses on the deliberate and accidental release of CBRN threats, including state-sponsored ones. It also addresses the technological advances in emerging technologies and their implications, particularly as regards the use and threat potential of AI and large language models. Given its sensitive nature, a short and non-classified overview is included.

Chapter III (antimicrobial resistance) addresses AMR, including bacterial, mycobacterial and fungal resistances. It provides an update on the AMR epidemiological

situation with a focus on the EU/EEA – including significant trends, unusual cases and outbreaks of AMR-related infections, as well as contextual events that favour the emergence and spread of AMR. Chapter III includes descriptions of the products that are currently in development to counteract the emergence of AMR in the most concerning pathogens, as well as the insufficient availability of antibiotics and other AMR MCM that the EU is facing and that can hinder the proper care of patients suffering from AMR infections.

Disclaimer: This Comprehensive Assessment takes into account existing and ongoing prioritisation exercises conducted by EU Member States, other Commission services and agencies, notably ECDC, global organisations and dedicated scientific networks. The European Commission will update its threat prioritisation during 2027, based on stakeholder feedback, in order to incorporate and reflect relevant prioritisation efforts. 'Time-sensitive' information (including information on the current MCM pipeline, authorised products or epidemiological situation) has been updated as on **5 October 2025**.

The information is provided for general purposes only. It does not constitute legal, professional or other advice.

CHAPTER I: VIRAL FAMILIES WITH EPIDEMIC AND PANDEMIC POTENTIAL

1. INTRODUCTION

There has been a growing shift in recent years towards prioritising entire virus families rather than individual viruses or strains. This broader perspective enhances preparedness and response capabilities – particularly against zoonotic viruses, variants of known viruses and the potential emergence of unknown pathogens ('Pathogen X' responsible for hypothetical 'Disease X').

HERA has, since its inception in 2021 and in line with this development, prioritised viral families rather than specific viral pathogens, considering priority and prototype pathogens within these families.

The latest update of the WHO priority list for epidemic and pandemic research preparedness was published in summer 2024 ([3]). It follows the same approach and also introduces the concepts of *priority pathogens* (pathogens that are expected to pose a significant public health threat) and *prototype pathogens* (representative pathogens from families with epidemic and pandemic potential) within each viral family. This represents a shift from WHO's HERA's previous 'priority diseases' approach.

This Comprehensive Assessment will further contribute to the key deliverable of "Develop[ing] an EU comprehensive risks and threats assessment" under the Preparedness Union Strategy ([4]), to support a coherent, forward-looking EU-level understanding of risks and threats, informing strategic planning, preparedness activities and coordinated response efforts across sectors and Member States.

2. METHODOLOGY

Various different approaches for pathogen prioritisation exist (including an ECDC tool for the prioritisation of infectious disease threats, which is currently being reviewed ([5])). However, a harmonised EU/EEA framework for prioritising threats to MCM preparedness and response has not yet been adopted.

The present prioritisation aims at identifying viral families that can cause serious cross-border threats to public health at EU level and could result in the recognition of a public

([3]) WHO, Pathogens prioritisation: a scientific framework for epidemic and pandemic research preparedness, July 2024 (https://cdn.who.int/media/docs/default-source/consultation-rdb/prioritization-pathogens-v6final.pdf)

([4]) JOIN(2025) 130 final: Joint communication to the European parliament, the European Council, the Council, the European Economic and Social Committee and the Committee of the Regions on the European Preparedness Union Strategy

([5]) ECDC tool for the prioritisation of infectious disease threats (https://www.ecdc.europa.eu/en/publications-data/ecdc-tool-prioritisation-infectious-disease-threats).

health emergency at EU level ([6]). It therefore requires EU interventions in the area of MCM.

The prioritisation was performed in two steps:

- identification of priority viral families using existing frameworks and priority lists, at EU and global level;
- an approximate assessment and prioritisation of viral families within the established list, based on the relevance of required MCM interventions to address these and related threats.

2.1. Identification of priority viral families

As a first step, existing lists in EU legislation were used to identify relevant agents, notably:

- the Commission Implementing Decision on communicable diseases covered by **epidemiological surveillance**, under which the ECDC collects, analyses and disseminates surveillance data from the EU Member States ([7]); and
- the human-health-relevant biological agents listed in the Commission Delegated Regulation on **dual-use items** ([8]).

From these lists, only agents classified in biosafety levels (BSL) / risk groups (RG) 3 and 4 according to Directive 2000/54/EC on the protection of workers from risks related to exposure to biological agents at work ([9]) were further considered. These agents pose a significant risk due to their potential to cause severe human disease, their potential for community spread and the limited availability of effective prophylaxis or treatments (especially RG 4 agents with high risk). Certain RG 3 biological agents were not included because they present only a limited risk of infection due to the fact that they are not normally infectious by the airborne route.

As a second step, to complement the identified agents of concern, additional sources from non-EU countries and international organisations were reviewed. These sources included both research-focused and preparedness-oriented priority lists (in accordance with HERA's work covering the full lifecycle of MCM relevant to the EU/EEA). The consulted sources, non-exhaustively, included:

- the WHO's priority list for epidemic and pandemic research preparedness (June 2024);
- the UK Health Security Agency's priority pathogen families research and development tool (March 2025);
- the US Department of Health and Human Services Tier 1 Select Agents list (2022);
- the US National Institute of Allergy and Infectious Diseases (NIAID) Biodefense Pathogens (2025);

([6]) Regulation (EU) 2022/2371 of the European Parliament and of the Council of 23 November 2022 on serious cross-border threats to health and repealing Decision No 1082/2013/EU.
([7]) Commission Implementing Decision (EU) 2018/945 of 22 June 2018 on the communicable diseases and related special health issues to be covered by epidemiological surveillance.
([8]) Commission Delegated Regulation (EU) 2023/2616 of 15 September 2023 amending Regulation (EU) 2021/821 of the European Parliament and of the Council as regards the list of dual-use items.
([9]) Directive 2000/54/EC of the European Parliament and of the Council of 18 September 2000 on the protection of workers from risks related to exposure to biological agents at work.

- the viral families prioritised by NIAID's USD 3.2 billion Antiviral Program for Pandemics (launched in June 2021);
- the Coalition for Epidemic Preparedness Innovations (CEPI) priority diseases list (2022).

HERA identified 12 priority viral families: *Arena-, Hanta-, Nairo-* and *Phenuiviridae* (these families are part of the viral order of *Bunyavirales*), as well as *Corona-, Filo-, Flavi-*, *Orthomyxo-, Paramyxo-, Picorna-, Pox-* and *Togaviridae*.

The priority viral families are represented in Figure 1 with an indication of the priority and prototype pathogens within these families.

All of the 12 viral families (but *Picornaviridae*) are associated with a *high* risk of PHEIC according to the 2024 WHO R&D Blueprint. The *Picornaviridae* viral family has also been included in the present Comprehensive Assessment because, while it is associated with a *medium* PHEIC risk, it is also necessary to consider the potential public health impacts of priority (polio) and prototype pathogens within this family (poliovirus and enteroviruses D71 and 68) and the relevance of MCM interventions to address these threats.

Figure 1. Overview of HERA's priority viral families and their representation in other frameworks and references of relevance.

HERA prioritisation	Viruses: Family (Genus)	Viruses: Agents	European legislative acts: CID(EU) 2018/945 ('epid. surveillance') (BSL3/4-refined)	European legislative acts: CDR(EU) 2022/1 ('dual use') (BSL3/4-refined)	international organisations: WHO R&D blueprint 2024: viral families with high 'PHEIC risk' (*)	2024: prioritypathogen (global)	2024: prototype pathogen (global)	2024: selected priority pathogens with circulation in WHO EURO region	2024: selected prototype pathogens with circulation in WHO EURO region	2018: R&D blueprint 'priority pathogens'	non-EU governmental entities & non-governmental organisations: US: US HHS Select Agents	US: US NIH NIAID's Biodefense Pathogens	US: US NIH NIAID's Antiviral Program for Pandemics (2021) (*)	UK: UK HSA priority pathogen families with both high epi- and pandemic potential (*)	CEPI: CEPI's priority viral families (*)
highest priority	***Coronaviridae*** *(Betacoronavirus)*	**Severe acute respiratory syndrome-related coronavirus (SARS-CoV)**	✓	✓		✓	✓	✓	✓	✓	✓				
		Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)		✓	✓	✓	✓	✓	✓		✓		✓	✓	✓
		Middle East respiratory syndrome coronavirus (MERS-CoV)		✓		✓	✓			✓					
	Orthomyxoviridae *(Influenzavirus A)*	**Influenza A virus (H1, H2, H3, H5, H6, H7, H10)**	✓	✓	✓	✓	✓ (H1, H5)	✓	✓ (H1, H5)			✓		✓	✓
		Influenza A virus A/New York/1/18 (H1N1) (Spanish flu 1918)	✓	✓							✓	✓			
	Flaviviridae *(Flavivirus)*	**Dengue virus**	✓			✓	✓	✓	✓			✓			
		West Nile fever virus	✓				✓		✓			✓			
		Tick-borne encephalitis virus (Far Eastern subtype)	✓	✓			✓		✓		✓	✓			
		Zika virus				✓	✓			✓		✓			
		Japanese encephalitis virus		✓	✓							✓	✓		
		Kyasanur Forest disease virus		✓							✓	✓			
		Omsk haemorrhagic fever virus		✓							✓	✓			
		Powassan virus		✓											
		Rocio virus		✓											
		Yellow fever virus	✓	✓								✓			
	Filoviridae *(Orthoebola- and Orthomarburgvirus)*	**Zaire ebolavirus**		✓		✓	✓			✓	✓	✓			
		Sudan ebolavirus		✓	✓	✓						✓	✓		✓
		Marburg marburgvirus		✓		✓				✓	✓	✓			
	Poxviridae *(Orthopoxvirus)*	**Monkeypox virus**		✓	✓	✓	✓	✓	✓		✓	✓			
		Variola (major and minor) virus	✓	✓		✓	✓				✓	✓			
high priority	***Paramyxoviridae*** *(Henipavirus)*	**Nipah henipavirus**		✓	✓	✓	✓			✓	✓	✓	✓	✓	✓
		Hendra henipavirus		✓						✓	✓	✓			
	Togaviridae *(Alphavirus)*	**Chikungunya virus**	✓	✓		✓	✓					✓			
		Venezuelan equine encephalomyelitis virus		✓	✓	✓	✓				✓	✓	✓		✓
		Eastern equine encephalomyelitis virus		✓							✓	✓			
		Western equine encephalomyelitis virus		✓								✓			
	Arenaviridae *(Mammarenavirus)*	**Lassa mammarenavirus**		✓		✓	✓			✓	✓	✓			
		Junin mammarenavirus		✓			✓				✓	✓			
		Lujo mammarenavirus		✓			✓				✓	✓			
		Brazilian mammarenavirus		✓	✓						✓				✓
		Chapare mammarenavirus		✓							✓	✓			
		Guanarito mammarenavirus		✓							✓	✓			
		Machupo mammarenavirus		✓							✓	✓			
	Phenuiviridae *(Phlebovirus)*	**Rift Valley fever phlebovirus**		✓		✓				✓	✓	✓			
		SFTS phlebovirus (severe fever with thrombocytopenia syndrome-virus)			✓	✓						✓			✓
	Hantaviridae *(Orthohantavirus)*	**Sin Nombre orthohantavirus**		✓		✓	✓					✓			
		Hantaan orthohantavirus		✓	✓			✓			✓				
		Choclo orthohantavirus		✓									✓		
		Dobrava-Belgrade orthohantavirus		✓	✓										
		Laguna Negra orthohantavirus		✓											
		Seoul orthohantavirus		✓											
	Nairoviridae *(Orthonairovirus)*	**Crimean-Congo haemorrhagic fever orthonairovirus**		✓	✓	✓	✓	✓	✓	✓	✓	✓			
	Picornaviridae *(Enterovirus)*	**EV-D68**			medium		✓		✓			✓			
		EV-A71					✓		✓			✓	✓	✓	
		Poliovirus, type 2										✓			

Priority viral families were identified in EU legislative acts (Commission Implementing Decision (EU) 2018/945 to be covered by epidemiological surveillance or human health-relevant biological agents listed in the Commission Delegated Regulation on dual-use items, further refined through their categorisation as either RG 3 or RG 4 agents, in line with Directive 2000/54/EC. Additional resources were used to refine the identification of viral agents and their respective families of concern. **Boldened agents** are specifically listed by the WHO either as priority or prototype pathogens. Disclaimer: This figure is intended for general informational purposes only; and may contain inaccuracies, omissions or inconsistencies. It does not constitute legal, professional or medical advice. No liability is accepted for any loss or damage arising from its use. Other viral families remain under consideration (notably *Peribunyaviridae*, with Oropouche virus as a known representative). This virus has demonstrated epidemic potential in tropical regions (particularly in South America) and has raised concerns over vertical transmission, congenital infection and foetal complications, which may lead to severe outcomes (including death). Further assessment is required in order to decide whether or not to include it in a future edition of HERA's priority list. Other viral families have not been prioritised, because they do not currently meet the criteria for higher epidemic and pandemic potential (including sustained human-to-human transmission, rapid cross-border spread and limited availability of effective countermeasures) and were therefore not captured by the applied filtering approach. These other viral families include *Retroviridae* (HIV), *Hepadnaviridae* (Hepatitis B), *Rhabdoviridae* (rabies), *Caliciviridae* (norovirus), *Reoviridae* (rotavirus), *Pneumoviridae* (RSV) and *Herpesviridae* (varicella). They are considered lower priority in HERA's current prioritisation context, but many remain under active surveillance by national and EU authorities (including the ECDC) due to their ongoing public health relevance. *(*) The prioritisation was applied at the viral family level where appropriate. The tick accordingly indicates the inclusion of the viral family rather than individual viruses. This is also visually reflected through a lighter green background.*

2.2. Assessment and prioritisation of viral families within the HERA list

The 12 priority viral families for HERA were divided into two subcategories: a group of **highest** priority viral families and a group of **high** priority viral families.

Threat-specific attributes of each viral family of concern were assessed (paying particular attention to the identified priority and prototype pathogens), notably (i) its epidemic and pandemic potential; (ii) its potential to cause an EU public health emergency at EU level; (iii) the availability of MCM; and (iv) the potential impact of climate change on the individual viral family.

2.2.1. Epidemic and pandemic potential

To better reflect the diversity of threat profiles, this document considers both the 'pandemic potential' and the 'epidemic potential' of pathogens. Pandemic potential refers to a pathogen's ability to cause widespread (often global) disruption. Epidemic potential captures those threats that may lead to large-scale, repeated or severe regional outbreaks (this is particularly relevant in the case of vector-borne diseases). This dual perspective ensures that prioritisation efforts adequately reflect both global and regionally significant threats.

All priority viral families identified by HERA are associated with the same *high* PHEIC risk according to the WHO. The one exception is *Picornaviridae*, which are associated with a lower ('medium') risk.

To inform further prioritisation, the present Comprehensive Assessment draws on a combination of attributes, including:

- **transmissibility** (i.e. a virus's ability to spread from person to person, commonly quantified by the basic reproduction number R_0 – while recognising the inherent limitations of the metric): higher transmissibility is (particularly in the case of airborne viruses such as *Coronaviridae* and *Orthomyxoviridae*) often associated with a higher epidemic and pandemic potential, hereby taking into account additional factors, too (e.g. population immunity, disease severity and contextual vulnerability; see also below). By contrast, viruses that require direct contact generally present a lower risk of widespread transmission;

- **mode of transmission**: airborne transmission (including spread via airborne droplets or aerosols) poses the greatest pandemic risk because it allows viruses to spread efficiently through the air and sometimes over long distances. More broadly, respiratory transmission, which includes both airborne and larger droplet-based spread ([10]), is highly significant because it enables widespread dissemination. Other routes (e.g. faecal-oral, vector-borne and direct contact) are generally associated

([10]) Aerosols are tiny particles (≤5 microns) that remain suspended in the air for long periods and can be inhaled deep into the lungs. They are key to airborne transmission (e.g. measles, tuberculosis and later SARS-CoV-2 variants). Small airborne droplets are slightly larger than aerosols but can remain airborne for some time, often behaving similarly to aerosols in indoor environments. Larger respiratory droplets include droplets >5–10 microns that fall quickly to the ground or onto surfaces. They typically require close-range exposure (e.g. influenza and earlier SARS-CoV-2 variants). The broad term 'respiratory transmission' includes both airborne and droplet transmission, as well as indirect spread via contaminated surfaces (fomites).

with a lower epidemic and pandemic potential but can still lead to major regional outbreaks or health emergencies (as evidenced by past Ebola virus outbreaks) and therefore remain significant in specific contexts;

- population **susceptibility and immunity**: a lack of population immunity correlates with higher epidemic and pandemic potential (e.g. new influenza viruses). The risk may be moderate if partial immunity already exists; the pandemic threat can be considered to be lower for pathogens for which high seroprevalence or vaccine-induced immunity is present;

- **pathogenicity** (i.e. the virus's ability to cause disease in an infected host): this determines the severity of the clinical outcomes of an infection, ranging from mild symptoms to severe illness and death. It can be determined through the case fatality rate.

2.2.2. Potential for public health emergency at EU level

The potential for causing a **serious cross-border health threat requiring EU-level coordination and intervention on MCM** (including the possible recognition of a public health emergency at EU level) was assessed on the basis of the history and epidemiology of the concerned pathogens, including their presence in the EU (e.g. localised outbreaks, cross-border epidemics and imported cases), patterns of international spread, the current epidemiological situation and associated health burden within the EU, and available risk assessments by the ECDC.

Consideration was also given to available resources on the EU's readiness to respond to imported cases of high-consequence infectious disease pathogens, such as those causing viral haemorrhagic fevers ([11]).

2.2.3. MCM availability

The **availability** of **vaccines** and **therapeutics** for the prototype pathogens within the viral family was described for this Comprehensive Assessment as one of the following:

- 'available': a threat-specific vaccine or therapeutic has been developed and has been granted marketing authorisation within the EU with an approved indication for use against the prototype pathogen(s) of that viral family;
- 'limited': EU-authorised vaccines/therapeutics exist against some but not all prototype pathogens of the family, or only symptomatic and supportive care but no threat-specific is available;
- 'not available': no EU-authorised vaccines/therapeutics exist.

2.2.4. Impact of climate change

Outbreaks of infectious diseases (particularly zoonoses and vector-borne diseases) have increased over time and are expected to continue increasing in line with ongoing climate change. Climate change is an essential risk factor as regards pathogen spillover, because

([11]) ECDC: Health emergency preparedness for imported cases of high-consequence infectious diseases. October 2019 (https://www.ecdc.europa.eu/sites/default/files/documents/Health-emergency-preparedness-imported-cases-of-high-consequence-infectious-diseases.pdf)

shifting environmental conditions alter habitats, species ranges and population densities (leading to new interactions between species) and increase the risk of zoonotic emergence. Adjacent environmental factors (e.g. water contamination and poor sanitation) can also make individuals more susceptible to infectious diseases and facilitate the spread of pathogens.

Europe is experiencing a warming trend. Heat waves and flooding are becoming more frequent and severe, and summers are becoming longer and warmer. Research indicates that almost two thirds of European human and domestic animal pathogens are sensitive to climate variables ([12]).

This present Comprehensive Assessment therefore also considers the **impact of climate change** for each of the identified priority viral families, starting with the following general considerations.

2.2.4.1. Vector-borne diseases

In the context of this report, vector-borne diseases are diseases transmitted by arthropod vectors (e.g. mosquitoes, ticks and sand flies). Warmer temperatures and altered precipitation patterns are altering the density of arthropod vectors, their geographic distribution and their seasonal activity. These combined factors have led to the emergence and re-emergence of vector-borne diseases in Europe, including dengue fever, West Nile virus infection, Crimean-Congo haemorrhagic fever (CCHF) and tick-borne encephalitis.

International human mobility and climate change have helped some vectors (notably *Aedes* mosquitoes) to rapidly spread around the world. *Aedes albopictus* (a competent vector for dengue, chikungunya and zika) was absent from the EU until 1990 but is now established in all Mediterranean EU Member States and is expanding northward (it is established in Germany, Hungary and Slovenia and had been detected in Belgium, the Netherlands and Sweden ([13])). By contrast, *Aedes aegypti* (also a competent vector for these diseases) remains less widespread in Europe but has become established in Cyprus and Madeira.

2.2.4.2. Thawing permafrost

In 2025, an estimated 3 million people in the high northern latitudes were living on permafrost, where ongoing degradation is affecting critical infrastructure and increasing the risk of exposure to emergent biological threats.

The Arctic permafrost is a vast reservoir of poorly characterised microbial life, harbouring an extraordinary diversity of microbial and viral species even within small areas. These so-called '*Methuselah* microorganisms' have evolved a range of extremotolerant traits that have enabled them to survive for millennia in subzero temperatures with minimal water or nutrients.

Accelerated Arctic thaw is now revealing ancient microorganisms that are uniquely adapted to cold, anoxic environments. As they are reintroduced into modern ecosystems,

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([12]) Semenza J, Paz S. Climate change and infectious disease in Europe: Impact, projection and adaptation. Lancet Reg Health Eur. 2021 Oct 7;9:100230. doi: 10.1016/j.lanepe.2021.100230

- ([13]) ECDC: **Aedes albopictus - current known distribution: July 2024** (https://www.ecdc.europa.eu/en/publications-data/aedes-albopictus-current-known-distribution-july-2024).

they may interact with current microbial communities in unpredictable ways – potentially reshaping microbial communities, biogeochemical cycles and even disease dynamics. In this context, the combination of rapid Arctic environment change and permafrost thaw raises concerns about the possible re-emergence of ancient pathogens. Stable conditions in permafrost have, for example, preserved fragmented genomic material from variola virus (smallpox) and influenza viruses ([14]).

3. RESULTS - GENERAL OVERVIEW

The present section summarises the result of the prioritisation exercise and provides an overview of the families of concern and their prioritisation in Figure 2 followed by a summary for each viral family.

([14]) Wu et al.: Permafrost as a potential pathogen reservoir. Lancet, 2022. (https://doi.org/10.1016/j.oneear.2022.03.010)

Figure 2. Overview of the prioritised viral families, including an approximate mapping to relevant attributes.

HERA prioritisation	Viral family	PHEIC potential	EU cross-border threat potential, likelihood to require Union response	Transmissibility	Mode of Transmission	Population immunity	Pathogenicity	Global burden of disease	Burden of Disease in EU/EEA	Availability of vaccines	Availability of therapeutics
Highest priority	*Coronaviridae*	High	**Very high** (highly transmissible, novel strains, airborne; epi- and pandemic emergence)	**High** (airborne)	**Airborne** (aerosols and droplets); surface transmission negligible	**Moderate** (broad prior exposure, but waning immunity and variant escape reduce protection)	**Moderate to high** (SARS, MERS, COVID-19)	**High** (COVID-19 pandemic, impact of SARS and MERS)	**High** (COVID-19 waves, long-COVID impact)	**Available** (updated vaccines widely deployed; no universal coronavirus vaccine yet)	**Available** (e.g. Paxlovid, remdesivir); no broad-spectrum coronavirus antiviral yet available
	Orthomyxoviridae	High	**Very high** (airborne, seasonal variants, antigenic shifts maintain pandemic risk)	**High** (airborne)	**Airborne** (aerosols and droplets)	**Moderate to low** (highly dependent on viral strain, with likely no pre-existing immunity to a novel/pandemic strain)	**Moderate** (seasonal flu) **to high** (avian flu)	**High** (Seasonal flu, pandemic influenza events)	**High** (Seasonal flu significant, pandemic preparedness critical)	**Available** (Seasonal flu vaccines, pandemic preparedness)	**Available** (Antivirals like oseltamivir, baloxavir)
	Flaviviridae	High	**High** (vector-borne with expanding range; climate and travel increase risk of EU-wide transmission)	**Moderate** (vector-borne: primarily mosquito- and tick-borne, with rare non-vector transmission depending on the virus)	Primarily **vector-borne** (mosquito- and tick-borne); rare non-vector modes (e.g. vertical, sexual for Zika)	**Moderate** (partial and serotype-specific immunity depending on virus; vaccine-induced immunity for some flaviviruses)	**Moderate to high** (Dengue, Yellow Fever, Zika)	**High** (Dengue major global burden, Yellow Fever in Africa/South America)	**Moderate** (Dengue emerging in Southern Europe, TBEV endemic, Yellow Fever importation risk)	**Available** (Yellow Fever vaccines, Qdenga and Dengvaxia for Dengue; TBEV vaccine used in endemic EU regions)	**Limited** (antivirals in trials, supportive care)
	Filoviridae	High	**High** (importation risk through travel and lab exposure; high fatality risk and potential for severe outbreaks)	**Low** (contact with bodily fluids)	Primarily **direct contact** with body fluids; surfaces pose secondary risk	**Low** (sporadic outbreaks, limited exposure)	**High to very high** (depending on strain)	**Low to moderate** (limited outbreaks, but high mortality when outbreaks occur)	**Low** (very limited importation risk, few cases)	**Limited** (Ebola vaccines authorised with limited deployment; no vaccines for other strains, no pan-filovirus vaccine)	**Limited** (Monoclonals for Ebola, no broad-spectrum treatments; supportive care)
	Poxviridae	High	**Moderate to high** (MPXV outbreak, historical smallpox risk)	**Moderate** (primarily direct contact; droplets possible in close, prolonged exposure)	**Direct contact** with lesions, contaminated materials; respiratory droplets in close contact	**Low to moderate** (smallpox vaccine-derived immunity waning; mpox-specific immunity limited)	**Moderate** (Smallpox eradicated; mpox emerging with moderate morbidity and mortality)	**Moderate** (Smallpox historical, MPXV outbreaks increasing)	**Moderate** (MPXV outbreak in 2022, smallpox preparedness)	**Available** (Smallpox vaccine, MPXV vaccines)	**Available** (Cidofovir, tecovirimat for smallpox and MPXV)
High priority	*Paramyxoviridae**	High	**Moderate** (Nipah virus: zoonotic, high-fatality risk; potential for importation or spillover)	**Low** (Nipah/Hendra require close contact, limited sustained human-to-human transmission)	**Close contact** and zoonotic spillover (Nipah, Hendra)	**Low** (Population immunity negligible for Nipah and Hendra; no existing exposure or immunisation)	**High** (severe disease and high mortality in documented outbreaks)	**Moderate** (Nipah causes severe but localised outbreaks in endemic areas; Hendra extremely rare)	**Low** (no known cases to date; considered high-consequence if introduced)	**Not available**	**Limited** (supportive care only; no approved antivirals for Nipah or Hendra)
	Togaviridae	High	**Moderate** (Chikungunya autochthonous cases in southern Europe; EEEV/VEEV monitored, no EU cases to date)	**Moderate** (vector-borne; transmission depends on mosquito range, climate, and seasonality)	Primarily **vector-borne** (mosquito-borne); rare non-vector modes reported	**Low** (outbreaks in naïve populations; no widespread immunity or routine vaccination)	**Moderate to high** (Chikungunya causes chronic arthralgia; EEEV/VEEV may cause severe encephalitis with high CFR)	**Low to moderate** (Chikungunya endemic in tropics; EEEV/VEEV outbreaks in the Americas)	**Low** (Chikungunya cases in southern Europe; no documented EEEV/VEEV cases)	**Available** (Chikungunya vaccine authorised in EU; no licensed vaccine for EEEV/VEEV)	**Limited** (supportive care only; no approved antivirals)
	Arenaviridae	High	**Moderate** (Lassa: imported cases show risk via travel, lab exposure; requires high-level containment readiness	**Low to moderate** (mostly via rodent contact or contaminated materials; human-to-human transmission possible in outbreaks)	Primarily **rodent-borne**; human-to-human via body fluids possible in outbreaks	**Low** (sporadic regional exposure; no widespread immunity or vaccines in general population)	**High** (Lassa fever, haemorrhagic fevers)	**Low to moderate** (Lassa endemic in West Africa with tens of thousands of cases annually; other arenaviruses cause occasional outbreaks)	**Low** (sporadic imported Lassa cases; no local transmission)	**Not available**	**Limited** (ribavirin used for Lassa; no broadly approved antivirals for other arenaviruses)
	Phenuiviridae	High	**Moderate** (RVF importation risk; climate-driven vector spread raise potential for EU transmission)	**Low** (transmitted by mosquitoes or ticks; limited human-to-human transmission)	**Vector-borne** (mosquito or tick); possible **direct contact** with infected fluids	**Low** (sporadic outbreaks, limited immunity in most populations)	**High** (RVF, SFTS can cause haemorrhagic fever)	**Low to moderate** (RVF endemic in Africa; growing concern for SFTS in East Asia)	**Low** (rare RVF spillover; vectors present in some regions, but no local transmission)	**Not available**	**Limited** (supportive care; no approved antivirals)
	Hantaviridae	High	**Moderate** (endemic in rural EU; potential outbreaks require coordinated awareness and rodent exposure prevention)	**Low** (transmitted through aerosolised rodent excreta; rare human-to-human spread)	Primarily **rodent-borne** (inhalation of urine/droppings); rare **direct contact** transmission	**Low** (sporadic outbreaks, limited natural immunity)	**Moderate to high** (Hantavirus Pulmonary Syndrome and Haemorrhagic Fever with Renal Syndrome)	**Low to moderate** (Hantaviruses endemic in the Americas, Asia, and Europe; under-reported in rural areas)	**Low** (sporadic cases, primarily in rural forested areas; endemic strains present in Central and Northern Europe)	**Not available**	**Limited** (supportive care; no approved antivirals)
	Nairoviridae	High	**Moderate** (CCHF virus detected in southern Europe; travel-related cases and vector presence increasing)	**Low** (primarily tick-borne; limited transmission through direct contact with infected fluids)	Primarily **vector-borne** (tick-borne); possible contact with blood or tissues of infected animals or patients	**Low** (rare exposure and limited natural immunity)	**High** (Crimean-Congo Haemorrhagic Fever)	**Low** (CCHF outbreaks occur sporadically in Africa, Balkans, Middle East, and parts of Asia; localised, but severe)	**Low** (sporadic imported cases; Hyalomma ticks now established in parts of southern Europe, increasing risk of local transmission)	**Not available**	**Limited** (supportive care; no approved antivirals (ribavirin use remains inconclusive, not broadly approved))
	Picornaviridae	Medium	**Low to moderate** (poliovirus eradicated in EU; non-polio enteroviruses cause localised outbreaks, limited cross-border relevance)	**Moderate** (faecal-oral and respiratory routes; person-to-person transmission documented)	**Direct contact** (faecal-oral) and **respiratory**; environmental contamination contributes to spread	**High** (broad exposure to many enteroviruses; polio mostly eradicated, non-polio enteroviruses still circulating widely)	**Low to moderate** (mostly mild disease, with poliovirus and EV-D68 potentially causing severe neurological outcomes)	**Moderate** (polio a concern in some regions; enteroviruses causing larger numbers of mild infections, occasionally severe disease)	**Low** (polio eradicated; EV outbreaks occur sporadically but usually self-limiting)	**Available** (polio vaccines widely used; no vaccines for non-polio enteroviruses)	**Limited** (supportive care; no broad-spectrum antivirals for enteroviruses)

** Measles have been excluded because outbreaks within the EU/EEA result from reduced vaccination uptake, not intrinsic cross-border threat from viral evolution or emergence.*

This information was primarily derived from openly accessible resources; further details are provided in the main body of the report. *Disclaimer*: This figure is intended for general informational purposes only and may contain inaccuracies, omissions or inconsistencies. It does not constitute legal, professional or medical advice. No liability is accepted for any loss or damage arising from its use.

3.1. Viral families of highest priority

Taking the above criteria into consideration, *Coronaviridae, Orthomyxoviridae, Flaviviridae, Filoviridae* and *Poxviridae* have been identified as the ***highest priority*** viral families for HERA.

- ***Coronaviridae***

This viral family includes the highly pathogenic species MERS-CoV, SARS-CoV-1 and SARS-CoV-2. The *Coronaviridae* have been designated as posing a high PHEIC risk and are associated with a very high EU cross-border health threat potential. This is particularly due to their ability to transmit efficiently and the associated clinical risk, but also to the ongoing COVID-19 impact and the potential for future outbreaks driven by zoonotic spillovers or variant evolution.

Sustained human-to-human transmission through respiratory droplets and aerosols is well documented for SARS-CoV-1 and SARS-CoV-2, while MERS-CoV has been shown to have more limited human-to-human transmission – primarily in healthcare or household settings. This makes *Coronaviridae* one of the most worrying families for the EU/EEA from the pandemic potential perspective. Ongoing viral evolution (including immune escape variants of SARS-CoV-2) continues to pose challenges for control strategies.

Multiple vaccines and therapeutics for SARS-CoV-2 (including mRNA, vector-based and protein subunit vaccines) have received EU marketing authorisation. These products are periodically updated to reflect the variants that are currently circulating. While the adaptability of mRNA vaccine platforms has been demonstrated, challenges persist regarding coverage against emerging variants. SARS-CoV-2 continues to evolve under selective immune pressure and the resulting antigenic changes can reduce – but rarely eliminate – vaccine-induced protection, so vaccine formulations have to be regularly updated. Several antivirals and monoclonal antibodies have been authorised in the EU, but some therapeutics have proved less effective against newer variants.

No licensed vaccines or therapeutics exist for SARS-CoV-1 or MERS-CoV in the EU. Candidate vaccines for MERS-CoV are under development, but gaps remain in terms of manufacturing scalability and rapid-deployment capabilities.

Environmental and societal factors (including land-use alterations, global travel and increased contact between humans and animal reservoirs) may influence the likelihood of future zoonotic spillover events. Climate change is not a direct trigger, but it does shape ecological conditions (e.g. reservoir distribution, habitat disruption and species migration) that can facilitate virus emergence.

The demonstrated pandemic potential of *Coronaviridae* means that they remain a critical focus for EU and global preparedness planning.

- ***Orthomyxoviridae***

Orthomyxoviridae include the influenza A and B viruses. The WHO R&D blueprint has identified Influenza A viruses (such as subtypes H1, H2, H3, H5, H6, H7 and H10) as priority pathogens that are of the greatest concern from the pandemic risk perspective. The subtypes H1 and H5 have been designated as prototype pathogens, with H9N2 also being considered as a pathogen of concern.

Recent risk-assessment frameworks evaluating mammalian-adaptation markers in avian influenza viruses have identified a further 34 mutations associated with 5 phenotypic traits. Multiple adaptive mutations have most frequently been observed in A(H9N2), A(H7N9), A(H5N6) and A(H3N8) – and, in Europe, in H5Nx clade 2.3.4.4b viruses. Human infections remain rare, but most reported cases involve A(H5N1), A(H5N6), A(H7N9) or A(H9N2), which are also the subtypes that tend to accumulate the greatest number of adaptive traits ([15]).

Orthomyxoviridae (particularly influenza A viruses) have been designated as a high PHEIC risk. They are viewed as having a very high EU cross-border health threat potential due to the ability of influenza A viruses to transmit themselves via airborne respiratory routes, cause severe clinical outcomes and undergo frequent genetic changes. Influenza viruses evolve rapidly through antigenic drift and shift, which allows them to escape host immunity and limits the long-term effectiveness of vaccines. Seasonal influenza vaccine effectiveness varies between strains and seasons, but the effectiveness of neuraminidase inhibitors and baloxavir has remained constant stable, with only sporadic reports of reduced susceptibility. By contrast, widespread resistance has rendered adamantanes clinically obsolete.

One particular concern is the continuing evolution of highly pathogenic avian influenza (HPAI) A(H5Nx) clade 2.3.4.4b viruses (such as H5N1), which have recently shown that they can infect a wide range of mammalian species – including cattle, felines and humans ([16]). Sustained human-to-human transmission has not yet been observed, but the virus's expanded host range and capacity for genetic reassortment with seasonal or mammalian influenza strains heighten the risk of them adapting to new hosts and of new pandemic strains emerging. These developments underscore the need for enhanced genomic surveillance, One Health-based monitoring and pandemic-preparedness strategies.

Historically, pandemics in 1918 (H1N1), 1957 (H2N2), 1968 (H3N2) and 2009 (H1N1pdm09) demonstrated the capacity of *Orthomyxoviridae* to trigger global and European-level health emergencies – illustrating their high potential to trigger a public health emergency at EU level.

Climate change is not a direct cause of pandemic emergence, but it may influence influenza virus ecology by altering the migratory patterns of avian hosts, shifting seasonal transmission windows and increasing the frequency of human-animal interactions in new locations. These environmental changes modify risk and potentially influence the conditions for zoonotic spillover and virus spread.

- ***Flaviviridae***

Flaviviridae include several priority pathogens of global and regional significance – notably West Nile virus, yellow fever virus and dengue viruses. *Flaviviridae* have been designated as a high PHEIC risk. They carry a high EU cross-border health threat potential, particularly due to the expanding range of competent arthropod vectors. Their primarily

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([15]) ECDC/EFSA scientific opinion: Drivers for a pandemic due to avian influenza and options for One Health mitigation measures. March 2024. (https://efsa.onlinelibrary.wiley.com/doi/10.2903/j.efsa.2024.8735)

([16]) Buttinger G, Petrillo M, et al. Novel (d)PCR assays for influenza A(H5Nx) viruses clade 2.3.4.4b surveillance. Euro Surveill. 2025. 30(33):2500183. doi: https://doi.org/10.2807/1560-7917.es.2025.30.33.2500183.

vector-borne transmission limits their pandemic potential (compared with respiratory viruses), but dengue and other *flaviviruses* nevertheless remain serious public health threats due to their epidemic potential (especially in tropical and subtropical regions where large outbreaks are recurrent). The yearly increase in locally acquired (autochthonous) dengue cases in Europe is also a growing public health concern.

Few MCM against flaviviruses are available. Vaccines are authorised in the EU for dengue, yellow fever and tick-borne encephalitis viruses. No licensed human vaccines are currently available for zika or West Nile virus.

The WHO has identified dengue as one of the global priority endemic pathogens for vaccine research and development – given the need to implement awareness activities and ensure long-term, equitable access to approved products. Two dengue vaccines (Dengvaxia and Qdenga) have received EU marketing authorisation, but their utility in the context of a potential EU outbreak may be limited. Dengvaxia is only indicated for individuals with a documented prior dengue infection and is primarily intended for use in endemic settings. The discontinuation of its global production in 2025 will further reduce its availability. Qdenga has broader indications, but its efficacy varies across the four dengue virus serotypes and real-world data on its performance in non-endemic regions such as Europe remain limited. These factors may restrict the widespread implementation of dengue vaccines in the event of an outbreak in the EU.

No specific antiviral treatments are available for these viruses. Clinical management remains primarily supportive in nature.

The risk of flavivirus outbreaks in the EU is increasing, notably due to the established presence of competent vectors and the occurrence of autochthonous transmission of dengue (DENV), West Nile (WNV) and tick-borne encephalitis virus (TBEV) in several parts of the EU/EEA. However, the drivers of emergence vary between these viruses: the vectors of WNV (*Culex spp.*) and TBEV (*Ixodes ricinus*) are already established across much of Europe, but their presence alone does not equate to uniform outbreak risk, which depends on additional ecological and epidemiological factors such as vector competence, host abundance, temperature and population immunity. By contrast, the risk of dengue and zika outbreaks is closely linked to the expanding presence of *Aedes* mosquitoes (particularly *Aedes albopictus* and *Aedes aegypti*). The spread of these vectors is driven by climate change, land use change and urbanisation. Human travel contributes to the introduction of viruses into regions where competent vectors are already present, thereby creating conditions for local transmission.

- ***Filoviridae***

Priority pathogens within this family include Ebola virus (*species Zaire ebolavirus*, also classified as a WHO prototype pathogen), Sudan ebolavirus and Marburg virus, which are associated with a high EU cross-border health threat potential. Members of the *Filoviridae* family have been designated as a high PHEIC risk. They pose a significant health threat to humans due to their high case fatality rate and potential for rapid spread – even though this can be controlled in settings where contact tracing and isolation can be efficiently performed. These viruses continue to pose a significant public health challenge at the global level (as demonstrated by past outbreaks in sub-Saharan Africa). The risk of imported cases and secondary transmission into the EU remains low (because cases are likely to be promptly identified and isolated), but the high-consequence nature of these infections demands continuing preparedness and justifies their prioritisation in pandemic preparedness frameworks.

Progress has been made in developing vaccines and therapeutics for filoviruses, but challenges remain in terms of accessibility, production scalability and timely deployment.

Advances in monoclonal-antibody therapies such as Inmazeb and Ebanga (for Zaire ebolavirus) have improved treatment options. Two vaccines for Zaire ebolavirus (including a prime-boost regimen (Zabdeno/Mvabea) and a single-dose vaccine (Ervebo)), are authorised in the EU. However, vaccines against other viruses of this family are not available – despite recent advances in vaccine trials – and gaps remain in scalability and access to investigational vaccines.

Environmental factors (including climate change) may increase the risk of filovirus spillover events by altering ecological conditions that affect virus reservoirs (particularly fruit bats) and increasing the interface between human populations and wildlife. These factors do not directly trigger outbreaks, but they may influence the risk landscape by modifying conditions that are conducive to zoonotic spillover and thus increase human exposure risks.

- ***Poxviridae***

Priority pathogens within this family include variola (smallpox) virus – despite its eradication – and monkeypox virus, which is also a prototype pathogen. This viral family has been designated as a high PHEIC risk. It is associated with a moderate to high EU cross-border health threat potential, but its mode of transmission – direct contact – makes it less transmissible than airborne viruses.

MCM against poxviruses are available, with vaccines and treatments readily available to address the main representatives of this family. Smallpox vaccines (e.g. third-generation non-replicating vaccines) are available and are also indicated for use against mpox. Tecovirimat (an antiviral authorised for smallpox and mpox) is used under specific conditions for mpox, but emerging data have raised concerns about its efficacy against newer clades of the virus.

The 2022 mpox outbreak in Europe demonstrated these viruses' potential to cause public health emergencies in the EU. A further escalation occurred in 2024, when the WHO declared a PHEIC in response to the emergence and spread of a new mpox clade in the Democratic Republic of the Congo and neighbouring countries – further underlining the need for continuing preparedness against this disease and a coordinated international response. By mid-2025, WHO had reported sustained mpox transmission in Central Africa and limited imported cases in Europe – thus reinforcing mpox's status as a continuing global health threat.

While no deliberate release of smallpox virus has occurred in modern times and there is no indication of an imminent threat, preparedness strategies continue to consider smallpox as a high-consequence pathogen. This approach is consistent with EU-level guidance, including EMA's guidance on the use of medicinal products for treatment and prophylaxis in the event of exposure to biological agents used for terrorism, crime or warfare, which identifies smallpox as a pathogen of concern requiring preparedness measures ([17]).

([17]) https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/ema-guidance-use-medicinal-products-treatment-prophylaxis-case-exposure-biological-agents-used-weapons-terrorism-crime-or-warfare_en.pdf

Environmental changes (including climate change and ecosystem disruption) may influence the geographic distribution and behaviour of reservoir species, increasing opportunities for zoonotic spillovers of poxviruses. These should be understood as contributing risk factors rather than direct causes of emergence.

3.2. Viral families of high priority

Taking the above criteria into consideration, the seven following viral families have been identified as ***high priority*** for HERA.

- ***Paramyxoviridae***

Priority pathogens within this family include Nipah and Hendra viruses. They have been designated as a high PHEIC risk and are associated with a moderate EU cross-border health threat potential – considering the high case fatality rates and their ability to cause large outbreaks (particularly in South and South-East Asia).

There are currently no authorised MCM for Nipah virus in the EU.

The likelihood of *Paramyxoviridae* spreading within the EU/EEA is currently considered to be very low, particularly in the absence of their natural animal hosts. However, the virus remains a concern in endemic regions and is closely monitored due to its potential for severe disease and zoonotic spillover.

Environmental and ecological changes (including those influenced by climate change and land-use alterations) may affect bat ecology – thus increasing the frequency of spillover events and potentially extending transmission risks to livestock and humans. These factors can modify risk landscapes in endemic areas, but their impact on EU-level risk remains limited under current conditions.

- ***Togaviridae***

Priority pathogens within this family include the chikungunya virus and Venezuela equine encephalitis virus. *Togaviridae* have been designated as a high PHEIC risk. They are associated with a moderate EU cross-border health threat potential. They are primarily vector-borne, typically transmitted by mosquitoes such as *Aedes* spp. and generally exhibit slower and more localised transmission dynamics than respiratory viruses, but this does not necessarily equate to lower pandemic risk. Vector-borne transmission mechanisms may limit the speed of spread, but – under favourable environmental and ecological conditions – large-scale outbreaks and even regional epidemics remain possible.

MCM for togaviruses are limited, but vaccines are available for chikungunya virus (two vaccines were recently authorised in the EU: Ixchiq (live-attenuated) and VLA1553 (Valneva, authorised 2024)). However, no vaccine is available against the Venezuelan equine encephalitis virus or other viruses of this family and no treatment is currently authorised for togaviruses. Clinical management remains supportive, but antiviral and monoclonal-antibody candidates are still only in the early stages of development.

Togaviruses are not endemic to Europe, but autochthonous outbreaks of chikungunya virus have occurred in the EU (notably in Italy in 2007 and 2017) ([18])) and the virus continues

([18]) Local transmission of chikungunya virus in mainland EU/EEA, 2007–present.

to cause larger outbreaks in the EU's outermost regions (e.g. La Réunion and Martinique) and globally – thus underscoring its capacity to cause regional public health emergencies.

Venezuelan, Eastern and Western equine encephalitis viruses are not present in the EU but large outbreaks in the Americas (with periodic epidemic cycles in South and Central America) have highlighted the family's broader zoonotic potential.

There is an increasing risk of togavirus-related outbreaks in the EU (particularly chikungunya). This is due to the expanding geographic range of vector species (*Aedes albopictus* and *Aedes aegypti*) as well as climate-related factors that promote higher mosquito density and prolonged periods of vector activity. These conditions enhance the likelihood, intensity and duration of outbreaks in areas where competent vectors are already established. Such environmental shifts should be viewed as amplifying risk factors rather than direct causes of outbreak emergence.

- ***Arenaviridae***

Priority pathogens within this family include Lassa virus, Junin virus and Lujo virus, as well as Machupo and Chapare viruses, which are of regional concern in South America. This viral family has been designated as a high PHEIC risk. It is associated with a moderate EU cross-border health threat potential – notably due to the associated disease severity. However, the fact that transmission of these viruses primarily occurs through contact with rodent excreta or person-to-person transmission in healthcare settings makes them less transmissible than respiratory viruses.

In the EU, there is no specific MCM authorised against the priority pathogens of this family. The one exception is the use of ribavirin, which may offer benefit for Lassa fever under compassionate-use or off-label protocols.

A vaccine against Argentinian haemorrhagic fever (caused by Junin virus) is authorized for use in Argentina but is not authorised for use in the EU. Overall, MCM development for arenaviruses remains limited and is a recognised target area for global R&D investment.

The potential for Lassa or other arenaviruses to cause a public health emergency in the EU is low because the likelihood of autochthonous cases in the EU is very low. Preparedness against imported cases nevertheless remains important.

Environmental and climatic changes may influence the geographic distribution and population dynamics of rodent reservoir species, potentially altering transmission patterns. For example, climate shifts in parts of South America have been linked to changes in the range of rodents associated with Machupo and Chapare viruses (for example, into new areas of Bolivia). These factors are considered to be contributing risk modifiers, but their impact on EU-level threats remains limited.

- ***Phenuiviridae***

Priority pathogens within this family include the Rift Valley fever (RVF) and severe fever with thrombocytopenia syndrome (SFTS) viruses. These have been designated as a high PHEIC risk and are associated with a moderate EU cross-border health threat. There is no specific MCM authorised against pathogens of this family, but several vaccine candidates for RVF are in late-stage animal and early human trials.

Both the RVF and the SFTS viruses are currently absent from the continental Europe, but there have been several RVF outbreaks in EU overseas territories.

The RVF virus is primarily transmitted through mosquito vectors (especially the *Aedes* and *Culex* species), while the SFTS virus is transmitted via tick bites (mainly by the *Haemaphysalis longicornis* tick). Human infections may also occur through direct contact with the blood or tissues of infected animals.

The overall risk of RVF virus introduction via the animal trade or movement pathway is very low for all EU Member States. The incidence of the SFTS virus is continuing to increase in Asia, but its main vector (*Haemaphysalis longicornis*) has not been detected in Europe and no case of SFTS virus infection has been reported in the EU.

Environmental changes (including those associated with climate change) may contribute to the expansion of vector populations into previously unaffected geographic areas, thus potentially increasing the risk of virus emergence. Such environmental changes should be regarded as contributing risk factors that may alter future transmission dynamics (particularly in areas with ecological conditions that favour vector establishment).

- ***Hantaviridae***

Priority pathogens within this family include the Sin Nombre virus, which is also considered a prototype pathogen, and the Hantaan virus. This viral family has been designated as a high PHEIC risk and is associated with a moderate EU cross-border health threat potential (particularly as regards the high pathogenicity of certain representatives, including the Sin Nombre virus).

There are no authorised vaccines or treatments available in the EU against the pathogens of this family.

It is difficult to assess the risk of hantaviruses causing public health emergencies in the EU because hantavirus infections are underdiagnosed in many European regions. In addition, the respective role of different rodent species as virus reservoirs needs to be further assessed. The emergence of more pathogenic strains could, when combined with Europe's diverse rodent population, be a concern for the EU/EEA (particularly in rural and periurban areas where human-rodent contact is more frequent).

Environmental and land-use changes (e.g. deforestation, agricultural expansion and urban encroachment) bring human populations into closer contact with rodent habitats and increase human exposure to hantaviruses. These trends (including those linked to climate change) amplify the risk of hantavirus transmission, especially in areas where rodent populations are well established.

- ***Nairoviridae***

Priority pathogens within this family include the *Crimean Congo haemorrhagic fever* (CCHF) virus, which is also designated as a prototype pathogen. This viral family has been designated as a high PHEIC risk and is also associated with a moderate EU cross-border health threat potential.

The transmission of these viruses occurs primarily through tick bites and contact with infected bodily fluids. They are therefore less transmissible than respiratory viruses.

There are no authorised vaccines or antiviral treatments available against the CCHF virus or other viruses within this family. Clinical management remains supportive, with a focus on early detection and containment to prevent nosocomial transmission.

CCHF is endemic in parts of south-eastern Europe (notably in Bulgaria) and sporadic cases have been reported in Spain and Greece. This indicates the presence of endemic transmission focuses within the EU.

Climate change and land-use shifts may expand vector habitats, but it is essential to note that vector presence alone is not sufficient for CCHF to emerge in Europe. The virus's inherently low transmissibility and the absence of sustained transmission chains combine to keep the overall risk of a public health emergency low, even in areas where vectors are present.

- ***Picornaviridae***

Picornaviridae are associated with a low-to-moderate EU cross-border health threat potential. According to the WHO, there is a medium risk of them causing a PHEIC**.** Priority pathogens for the WHO EURO region include polioviruses (both wild and vaccine-derived). The enteroviruses (EV) D68 and A71 are considered to be prototype pathogens.

Vaccines against poliovirus (both inactivated [IPV] and oral [OPV]) are widely available and are the cornerstone of global eradication efforts. However, there are no authorised vaccines or antiviral treatments available against non-polio enteroviruses (including EV-D68 and EV-A71).

Poliomyelitis is a highly infectious disease but can be prevented by vaccination, which limits its potential to cause a public health emergency in the EU. However, if polio cases are detected or clear evidence of sustained community transmission emerges, the impact on public health services across EU/EEA countries would be substantial due to the containment and immunisation responses that would be required.

The incidence of the non-polio enteroviruses EV-D68 and EV-A71 is poorly defined due to limited systematic surveillance. However, these viruses have caused notable outbreaks in children in recent years, thus demonstrating that they can trigger public health emergencies in the EU and raising concerns about a change in the epidemiological pattern of these viruses in Europe.

Climate change is currently believed to have a limited influence on the transmission dynamics of picornaviruses. These viruses are primarily spread through faecal-oral and respiratory routes. Their seasonality is more due to human behaviour and indoor crowding patterns than to ecological drivers.

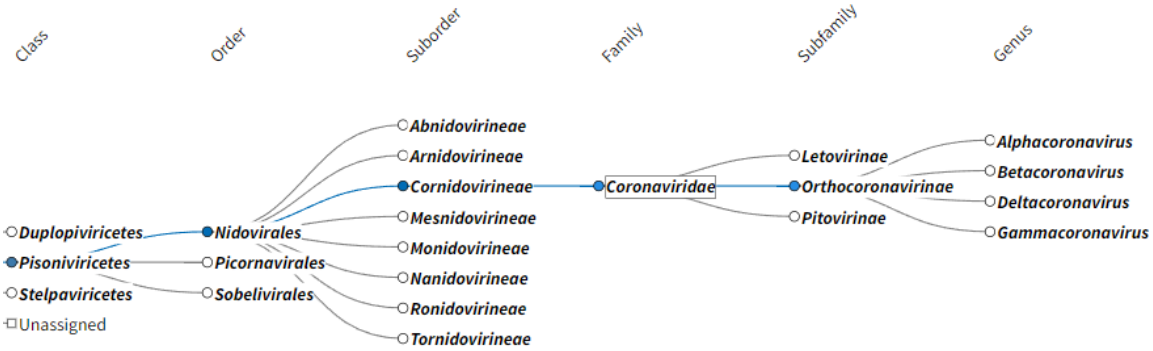
4. DETAILED DESCRIPTION OF THE GROUP 1 VIRAL FAMILIES: HIGHEST PRIORITY

In this section, each prioritised viral family of concern is described with:

- the family and its main viral representatives;
- the epidemiological situation globally and in the EU, the current associated health burden and risk assessments;
- the potential impact of climate change on this threat;
- the availability of threat-specific MCM (particularly vaccines and therapeutics).

Further information on the pathogens and viral families described below can be found in the ECDC disease factsheets ([19]), EFSA disease profiles ([20]) and WHO disease factsheets ([21]) and on the websites of other national and supranational public health entities.

4.1. Coronaviridae



([22])

4.1.1. Main representatives

Coronaviridae are a large family of viruses that cause respiratory and, in some cases, systemic infections in humans and animals. The viruses can be classified into four genera: *Alpha-, Beta-, Gamma-* and *Deltacoronavirus*. These genera are further divided into species based on their genetic and antigenic properties. Within each species, multiple variants can exist, each with unique characteristics that may impact transmissibility, pathogenicity and immune escape. This is particularly evident with SARS-CoV-2 variants, which have significantly shaped the global pandemic response.

At least seven coronavirus species have been identified as causing human infections. These include HCoV-229E, HCoV-OC43, HCoV-NL63, HCoV-HKU1, MERS-CoV (Middle East respiratory syndrome coronavirus), SARS-CoV-1 (severe acute respiratory syndrome coronavirus) and SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2). The WHO has identified *Sarbecoviruses* as priority pathogens.

([19]) https://www.ecdc.europa.eu/en/all-topics.
([20]) https://animal-diseases.efsa.europa.eu/.
([21]) https://www.who.int/news-room/fact-sheets.
([22]) The detailed description of the viral families incorporates visual elements from the *ICTV Visual Taxonomy Browser*, which is licensed under the Creative Commons Attribution-ShareAlike 4.0 International License. Proper attribution has been maintained. Any modifications or derivative content remain under the same licence.

MERS-CoV, SARS-CoV-1 and SARS-CoV-2 are designated as priority and prototype pathogens within the viral family, because they can cause severe outbreaks with high morbidity and mortality (as demonstrated by their respective pandemics and epidemics).

Human coronaviruses are globally prevalent and cause millions of infections annually. The epidemiology of these viruses varies depending on the specific species. MERS-CoV, SARS-CoV-1 and SARS-CoV-2 have emerged from animal reservoirs and caused international outbreaks.

Transmission typically occurs via respiratory droplets from an infected person (droplet transmission) and, less frequently, through contact with contaminated surfaces (fomite transmission).

4.1.2. Epidemiological situation

SARS-CoV-1

SARS-CoV-1 caused an outbreak in 2002-2003 that originated in Foshan in Guangdong Province, China. It then spread globally, with over 8 000 known cases across 33 countries on five continents within eight months. 21% of these cases occurred in healthcare workers ([23]). The estimated case fatality rate was approximately 10%. The latest known community case occurred in the US in July 2003, but a limited animal-to-human transmission event was documented in 2004.

International surveillance has continued, but no human infections with SARS-CoV-1 have been reported anywhere in the world since 2004.

SARS-CoV-2

The first cases of COVID-19 were reported in Europe in January 2020. The virus has since continued to evolve and circulate across the continent. As of October 2025, there have been over 240 million confirmed cases of COVID-19 in the EU, with more than 2.1 million reported deaths. The situation remains dynamic, with ongoing genetic diversification and the emergence of antigenically distinct variants.

As of October 2025, Omicron and its sublineages remain the predominant drivers of SARS-CoV-2 transmission in the EU/EEA. WHO global surveillance indicates that the XFG lineage accounted for ~68% of submitted sequences as of October 2025, followed by NB.1.8.1 at ~20%. XFG and NB.1.8.1 are not currently assessed as posing a substantially greater risk than other circulating lineages.

BA.2.86 (Pirola) was previously under scrutiny, but its prevalence has declined and there is no convincing evidence that it is more transmissible or severe than earlier Omicron subvariants. Attention has shifted to sublineages such as XEC, LP.8.1.1 and other entities within the XBB family that exhibit moderate antigenic drift and partial immune escape.

Despite the continuing presence of the virus, high levels of population immunity – achieved through a combination of previous infections, vaccinations and booster campaigns – have significantly reduced the overall severity of the disease compared with earlier phases of the pandemic. However, vulnerable populations (e.g. older people,

([23]) ECDC: Severe acute respiratory syndrome (SARS) - Annual Epidemiological Report for 2015.

immunocompromised individuals and those with underlying health conditions) remain at higher risk of severe outcomes.

Maintaining high vaccination coverage (especially with updated formulations that target currently circulating subvariants) remains a key public health priority for mitigating the impact of future waves.

MERS-CoV

MERS-CoV remains endemic in dromedary camels in the Middle East and most primary human infections are associated with zoonotic transmission through direct or indirect contact with infected animals. Bats are also considered as potential reservoirs. The virus has not been identified in animal hosts within Europe. Limited human-to-human transmission has been observed within healthcare settings in the Middle East, but sustained human-to-human transmission has not yet occurred.

Only sporadic travel-associated cases have been recorded in the EU/EEA, where the most recent confirmed case was reported in 2019. As of October 2025, no autochthonous transmission or secondary outbreaks have been documented.

The probability of MERS-CoV being introduced into the EU/EEA is low, but its high case fatality rate (~35%) and nosocomial outbreak potential justify its continued prioritisation in preparedness planning.

Other human coronaviruses

The endemic human coronaviruses HCoV-229E, HCoV-OC43, HCoV-NL63 and HCoV-HKU1 are responsible for a substantial proportion of mild to moderate respiratory illnesses worldwide and are typically associated with seasonal circulation. These viruses account for an estimated 15% to 30% of common colds in adults. They typically cause self-limiting upper respiratory symptoms but can result in lower respiratory tract disease or complications in high-risk groups (e.g. infants, older people and immunocompromised individuals).

4.1.3. Impact of climate change

Climate change is shaping the ecological and environmental conditions that influence the emergence and transmission of coronaviruses (including zoonotic members of the *Coronaviridae*). These viruses are primarily hosted by wildlife (especially bats) but can also infect a wide range of mammalian species (including livestock and humans).

Climate-driven changes (such as rising temperatures, altered precipitation patterns, deforestation and the increasing frequency of extreme weather events) are reshaping habitats and species distributions. Bat populations may shift their geographic ranges in response to habitat loss or changing climate conditions, potentially increasing their proximity to human settlements. Such shifts do not directly cause viral emergence, but they can increase the risk of zoonotic spillover by creating more frequent or new interfaces between wildlife, domestic animals and humans.

Land-use changes (including urbanisation, agricultural expansion and forest degradation) further amplify these interactions, increasing the likelihood that coronaviruses circulating in natural reservoirs may spill over into intermediate hosts (e.g. camels in the case of MERS-CoV) and, under the right conditions, infect humans.

Climate-related disruptions (e.g. food insecurity, displacement and rapid urbanisation) can strain healthcare infrastructure and increase the vulnerability of human populations to infectious disease outbreaks. These cascading effects of climate change may not only contribute to the risk of virus emergence but also hinder timely detection and containment.

4.1.4. MCM availability

Vaccines against SARS-CoV-2

As of October 2025, several COVID-19 vaccines employing various platform technologies were authorised for use in the EU.

- **mRNA vaccines**

Comirnaty (Pfizer-BioNTech) and **Spikevax** (Moderna) deliver lipid-nanoparticles-encapsulated mRNA that encodes the SARS-CoV-2 spike protein. Both have variant-adapted formulations authorised for Omicron BA.1, BA.4-5, XBB.1.5 and, most recently, the JN.1 and KP.2 subvariants.

ARCT-154 (Kostaive) is a self-amplifying mRNA vaccine that received EU marketing authorisation in February 2025. EPAR data indicate that neutralising responses are not inferior to those of first-generation mRNA boosters when using a lower mRNA dose. As of October 2025, ongoing post-authorisation surveillance was confirming favourable safety and immunogenicity profiles.

- **Viral-vector vaccines**

Jcovden (Johnson & Johnson) and **Vaxzevria** (AstraZeneca) were originally authorised, but their EU marketing authorisations were withdrawn at the sponsors' request on 9 August 2024 and 27 March 2024 respectively. No new vector-based COVID-19 vaccines are currently under evaluation in the EU.

- **Protein subunit vaccines**

Bimervax (HIPRA) is authorised as a booster in individuals ≥16 years and contains a recombinant RBD fusion (Alpha and Beta) with SQBA adjuvant.

VidPrevtyn Beta (Sanofi Pasteur) was withdrawn on 11 March 2024 at the market authorization holder's (MAH) request.

Nuvaxovid (Novavax) is an adjuvanted recombinant spike protein vaccine that received approval in October 2024 for an updated XBB.1.5 formulation in persons ≥12 years. An additional KP.2-adapted version was submitted to the European Medicines Agency (EMA) for evaluation in September 2025.

- **Inactivated virus vaccines**

VLA2001 (Valneva) lost its EU authorisation on 12 October 2023 for commercial reasons. As of October 2025, no inactivated SARS-CoV-2 vaccine held EU marketing authorisation.

Therapeutics against SARS-CoV-2

Vaccines remain the primary means for preventing COVID-19, but therapeutics also play a role. Therapeutic approaches for COVID-19 can be broadly categorised into three main types: (1) **direct-acting antivirals**, which target specific components of the SARS-CoV-2

virus to prevent its replication and spread in the body; (2) **monoclonal antibodies**; and (3) **immunomodulators**.

Several therapeutic options have been approved in the EU for the prevention and treatment of COVID-19 and others are under development. These include the following.

- **Direct-acting antivirals**

Nirmatrelvir/Ritonavir (Paxlovid, Pfizer) is an oral antiviral authorised for early treatment in adults and adolescents. Updated product information in 2024 noted reduced *in vitro* activity against certain Omicron sublineages, but clinical effectiveness remained favourable.

Remdesivir (Veklury; Gilead Sciences Ireland UC) is an intravenous antiviral authorised for hospitalised and early out-patient use. Its efficacy is greatest when started ≤7 days after symptom onset.

Molnupiravir has not received EU marketing authorisation and was no longer under active EMA evaluation as of October 2025.

- **Monoclonal antibodies**

Tixagevimab/cilgavimab (Evusheld; AstraZeneca) retains EU authorisation for pre-exposure prophylaxis in immunocompromised individuals, but its clinical utility is limited by the markedly reduced neutralisation of circulating Omicron subvariants.

Sipavibart (Kavigale; AstraZeneca) was authorised on 20 January 2025 for pre-exposure prophylaxis in immunocompromised individuals. EPAR data as of October 2025 indicate sustained neutralising activity against current Omicron subvariants.

Regkirona (regdanvimab; Celltrion Healthcare), **Ronapreve** (casirivimab/imdevimab; Regeneron and Roche), and **Xevudy** (sotrovimab; GSK) are still authorised. However, they show limited neutralising activity against currently circulating variants and are no longer recommended by ECDC clinical-management guidance.

- **Immunomodulators**

Tocilizumab (RoActemra; Roche Pharma AG) is an IL-6 receptor blocker indicated for severe COVID-19 with evidence of systemic inflammation.

Kineret (anakinra; Swedish Orphan Biovitrum AB (Sobi)) is an IL-1 receptor antagonist authorised for severe COVID-19 pneumonia in adults requiring supplemental oxygen.

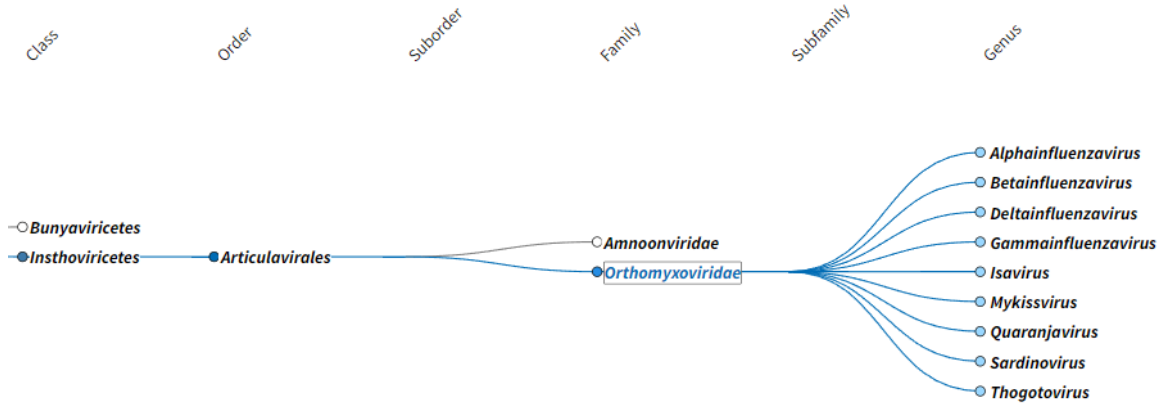
Vilobelimab (Gohibic; InflaRx GmbH) is an anti-C5a antibody that was granted conditional authorisation in 2024 for critically ill patients. This conditional authorisation was renewed in 2025 following confirmatory data.

Dexamethasone is a corticosteroid recommended for patients requiring respiratory support. It was still a part of WHO-endorsed standard of care as of October 2025.

Vaccines and therapeutics against other members of the *Coronaviridae* family

There are currently no approved vaccines or therapeutics for MERS-CoV, SARS-CoV-1 or endemic human coronaviruses (HCoV-229E, HCoV-OC43, HCoV-NL63 and HCoV-HKU1) as of October 2025. However, two MERS-CoV vaccine candidates (ChAdOx1-MERS and INO-4700) were in Phase III trials under CEPI-WHO collaboration.

4.2. *Orthomyxoviridae*



4.2.1. Main representatives

The influenza viruses are the main representatives of *Orthomyxoviridae*. There are four relevant types that belong to different genera: influenza A virus (IAV, *Alphainfluenzavirus*), influenza B virus (IBV, *Betainfluenzavirus*), influenza C virus (ICV, *Gammainfluenzavirus*) and the more recently discovered influenza D virus (IDV, *Deltainflunezavirus*). IAV has the widest host range, with aquatic birds (waterfowl, *anseriformes*) serving as its major natural reservoir. IBV mainly infects humans, but sporadic infections in seals have been described. ICV and IDV primarily circulate in humans, cattle and pigs. ICV causes typically mild respiratory illness in humans and, while it can also infect pigs, has limited genetic diversity and is not important from the public health perspective. IDV is widespread in cattle and also infects pigs. According to the WHO, there was no confirmed evidence of human IDV infections as of October 2025.

Influenza ('flu') is a contagious respiratory illness. Seasonal epidemics of influenza are caused by virus types A and B, which are endemic in humans in the EU and worldwide. Only IAV is known to cause global pandemics. Influenza viruses are transmitted through respiratory droplets caused by sneezing, coughing or talking. They are present in the population year-round but mainly cause seasonal epidemics mainly during the winter season in the northern hemisphere. The severity of influenza outbreaks varies from year to year, depending on the circulating influenza virus strains and the level of immunity in the population. The influenza virus has significant epidemic and pandemic potential because it can mutate and reassort between human, avian and swine strains, and this ability can in turn lead to new strains that spread quickly across populations with little pre-existing immunity. Seasonal influenza vaccination campaigns ahead of the anticipated winter epidemic in the northern hemisphere are part of the immunisation programme of all EU Member States. These campaigns target individuals to differing degrees according to their age, any existing health conditions that put them at risk of severe disease and occupational risk.

Influenza A viruses are further classified into subtypes based on the surface proteins hemagglutinin (H) and neuraminidase (N). H1N1 and H3N2 are the most common subtypes of influenza A virus that cause human infections. The WHO R&D blueprint has identified subtypes such as H1, H2, H3, H5, H6, H7 and H10 as priority pathogens. H9N2 is also considered a pathogen of concern. Influenza B viruses exist as two different lineages: B-Yamagata and B-Victoria. Circulation of B-Yamagata in humans has been extremely limited since early 2020 and it may be functionally extinct, but WHO and ECDC are still monitoring it. These types and subtypes of the virus are adapted mainly to humans and are responsible for 'seasonal influenza'.

Avian influenza (commonly known as 'bird flu') is a viral infection caused by other subtypes of influenza A and affects wild birds and poultry. Avian influenza A viruses are maintained in bird populations, but some avian-origin strains can occasionally infect mammals. By contrast, influenza A viruses that are now fully adapted to other mammals (such as the equine H3N8 and historically equine H7N7 lineages or the diverse swine H1 and H3 lineages) circulate independently within their respective hosts and are not classified as avian influenza viruses. Transmission to humans is relatively rare and typically occurs either through direct contact with infected animals or their bodily fluids, or through exposure to contaminated environments. However, cross-species transmission (including from mammals to humans) is a public health concern – not only due to the potential severity of the disease but also due to the potential for virus adaptation to the new infected species or risk of reassortment that could lead to the emergence of a new pandemic strain.

Multiple subtypes of avian influenza A viruses can have epidemic and pandemic potential. The H5, H7 and H9 subtypes are of greatest overall concern due to combined criteria relating to infection likelihood severity and human-to-human transmission. A(H7N9) and A(H9N2) were assigned the highest overall likelihood scores for zoonotic infection. A(H5N1), A(H5N6) and A(H7N9) received the highest impact scores due to high case fatality rates among recorded human infections ([24]). These risk assessments estimate the pandemic potential by integrating data on transmissibility, host adaptation and severity.

In the EU/EEA, H5Nx viruses belonging to clade 2.3.4.4b have caused more mammalian infections than other avian influenza clades currently circulating in Europe and globally. This is largely due to their widespread circulation in wild birds and poultry worldwide. These viruses have frequently acquired adaptive traits such as enhanced polymerase activity and immune evasion, but mutations affecting receptor specificity remain rare ([25]).

Globally, human infections remain uncommon. Most cases recorded between 2003 and October 2025 were associated with subtypes A(H5N1), A(H5N6), A(H7N9) and A(H9N2). All of them tend to exhibit a higher accumulation of adaptive features over time ([26]).

Historically, clinical presentations of individuals infected with A(H5N1) – also including clades other than 2.3.4.4b – have ranged from asymptomatic or mild (such as conjunctivitis and upper respiratory tract symptoms) to severe illness resulting in death. Case fatality since 2003 has been estimated at 48%, but this figure can only be based on reported cases and may be overestimated.

Some subtypes, such as A(H9N2), generally exhibit lower case fatality rates than A(H5N1) or A(H7N9). Available antiviral medications against seasonal influenza viruses are also currently considered effective against influenza viruses across all subtypes (including zoonotic strains) when administered at an early stage of infection.

Vaccines for avian influenza are available in for specific strains and populations. Authorised products in the EU/EEA are used in adults to protect against flu caused by the

([24]) WHO TIPRA framework (Yamaji et al., 2024) and the joint ECDC/EFSA Scientific Opinion (2024).
([25]) ECDC/EFSA Scientific Opinion on 'Preparedness, prevention and control related to zoonotic avian influenza', January 2025.
([26]) ECDC/EFSA Scientific Opinion on 'Preparedness, prevention and control related to zoonotic avian influenza', January 2025.

H5 strains of the influenza A virus. No pre-pandemic vaccines specifically targeting H7 or H9 were currently authorised in the EU/EEA as of October 2025.

The other *Orthomyxoviridae* include the *Thogoto-*, *Quaranja-*, *Sardino-*, *Mykiss-* and *Isa-viruses*. These viruses are not considered as priority pathogens within this family.

4.2.2. Epidemiological situation

Each year, seasonal influenza causes up to 50 million symptomatic cases in the EU/EEA, with an estimated 15 000 to 70 000 deaths attributed to influenza-related complications ([27]).

Globally, zoonotic influenza continues to pose a sporadic threat. Between 2003 and mid-2025, the WHO reported more than 980 laboratory-confirmed human cases of avian influenza A(H5N1), including around 473 deaths (case fatality rate ~ 48%) ([28]). Most transmissions stem from poultry or environmental exposure. No sustained human-to-human transmission spread has been confirmed.

Between March 2024 and early 2025, the United States recorded around 70 laboratory-confirmed human infections with clade 2.3.4.4b, including one fatality. Most cases (~40) were associated with exposure to infected dairy cattle (genotype B3.13), while a smaller number were linked to infected poultry (genotype D1.1).

Several human infections have been reported in the same time period in Cambodia, Mexico and Vietnam that were associated with clade 2.3.4.4b strains or reassortants of 2.3.4.4b with other avian influenza viruses circulating in birds in the area. The Mexican case was reported in April 2025 and involved a child fatality.

Within the EU/EEA, no human cases of HPAI A(H5N1) had been reported as of October 2025. According to the ECDC, at the time of this report, the risk of infection for the general public is low, rising to low-to-moderate for those individuals with direct exposure (e.g. occupationally) to infected animals or contaminated environments ([29]).

Influenza viruses are prone to rapid evolution and wide avian circulation, so further sporadic zoonotic cases remain possible – particularly among individuals with high animal contact, such as farmers, poultry workers and veterinarians. Continuing surveillance of influenza viruses in wild birds, poultry, mammals and people worldwide, and frequent reassessments remain critical to determining the public health risk, along with ongoing preparedness efforts. Contributing to this preparedness action, the European Commission's Joint Research Centre (JRC) has (in collaboration with the European Union Reference Laboratory (EURL) for Avian Flu and Newcastle disease, the Belgian (Sciensano) and the Italian (Istituto Superiore di Sanità) National Reference Laboratories) developed two digital RT-PCR assays to monitor the insurgence of new outbreaks and eventually the spread of highly pathogenic influenza A(H5Nx) clade 2.3.4.4b viruses ([30]).

The evolving situation (particularly in locations like the United States, where dairy cattle have become a new transmission interface) requires continuing virological surveillance,

([27]) ECDC: Factsheet about seasonal influenza.
([28]) WHO Disease Outbreak News, Avian Influenza A(H5N1).
([29]) ECDC: Avian influenza overview June-September 2025.
([30]) Buttinger G, Petrillo M, et al. Novel (d)PCR assays for influenza A(H5Nx) viruses clade 2.3.4.4b surveillance. Euro Surveillance, 2025, 30(33):2500183, doi: https://doi.org/10.2807/1560-7917.es.2025.30.33.2500183.

farm biosecurity reinforcement and occupational protection protocols. Concerns remain about potential viral adaptation to mammals.

4.2.3. Impact of climate change

Climate change is influencing the ecology, epidemiology and transmission dynamics of influenza viruses by altering the ecology of virus reservoirs and its natural animal hosts (including their migration patterns), thereby affecting virus transmission and human-animal interactions. Rising global temperatures, changing precipitation patterns, extreme weather events and ecosystem disruptions are affecting the distribution, abundance and behaviour of reservoir and intermediate host species, thereby shaping the circulation and geographic spread of orthomyxoviruses.

The main climate-related and environment-related pandemic drivers include: (i) changes in wild bird migration routes and congregation sites, particularly along the East Atlantic and Mediterranean flyways; (ii) increased mixing of wild and domestic bird populations due to habitat loss, droughts and flooding; and (iii) expansion of competent vector and host species linked to milder winters and altered precipitation regimes. These shifts are increasing the opportunities for cross-species transmission and viral reassortment ([31]).

Changing migratory bird patterns under warmer conditions are already altering the seasonal timing and geographic extent of avian influenza outbreaks. Extreme weather events can increase interactions between wild and domestic birds, heightening pandemic risks by increasing the opportunities for human exposure and the risk of human infection and virus adaptation to humans.

Stress in livestock due to heat may lead to immunosuppression, potentially increasing virus circulation in pigs and cattle. Climate-driven shifts in livestock production systems (including intensified poultry and swine farming in newly favourable regions) further increase the risk of reassortment and zoonotic spillover. Climate-driven shifts in livestock production systems and heat stress in cattle may increase viral spread and the risk of zoonotic transmission.

In human populations, increased indoor crowding during heatwaves or storms may facilitate the transmission of seasonal influenza. Warmer winters and extreme weather may alter virus behaviour in ways that cannot be fully anticipated and this may in turn affect the seasonality of influenza.

Recent evidence shows that avian influenza viruses such as H5N1 have already crossed species barriers (for example, in fur animal farms), but there have not been any reported human infections in the EU/EEA. However, evolving viral traits – especially those enhancing replication or immune evasion – are being detected and these highlight the need for integrated One Health approaches that combine animal surveillance, environmental monitoring and public health preparedness to mitigate future pandemic risks ([32]).

([31]) ECDC/EFSA joint Scientific Opinion 'Drivers for a pandemic due to avian influenza and options for One Health mitigation measures' (2024).

([32]) ECDC/EFSA report: Drivers for a pandemic due to avian influenza and options for One Health mitigation measures. April 2024.

4.2.4. MCM availability

Vaccines against seasonal influenza

Three main types of influenza vaccines have been authorised in the EU: (1) inactivated influenza vaccines (IIVs), which are whole-virus, split or subunit products that trigger antibody production against viral surface antigens (examples include Fluad Tetra and Flucelvax Tetra (Seqirus)); (2) recombinant protein-based vaccines that are produced via DNA-engineered systems to express viral surface proteins (examples include Supemtek Tetra (Sanofi)); and (3) live-attenuated influenza vaccines (LAIVs), which contain genetically weakened but replication-competent influenza viruses that are cold-adapted and temperature-sensitive, allowing limited replication in the nasopharyngeal mucosa but not in the lower respiratory tract (examples include Fluenz Tetra (AstraZeneca)).

In addition to centrally EU-level authorized vaccines, seasonal influenza vaccines with national marketing authorisation in the EU/EEA are manufactured by Abbott (Influvac, Influvac Junior, Influvac Tetra, Batrevac and Batrevac Tetra), GSK (Fluarix and Influsplit in both trivalent and quadrivalent forms), Sanofi Pasteur (Vaxigrip, Vaxigrip Tetra, Vaxigrip Infants, Mutagrip and Efluelda) and Seqirus (Fluad, Fluad Tetra and Afluria Tetra). These vaccines are authorised for use across various age groups and are formulated to match the seasonal influenza strains that are recommended annually. Some quadrivalent formulations may be phased out in the future following EMA guidance on the declining relevance of the B/Yamagata lineage.

Vaccines against avian influenza

Zoonotic vaccines are intended for immunisations during outbreaks of avian influenza in animals) to protect the most exposed individuals (e.g. occupationally exposed people like poultry workers or veterinarians) or vulnerable populations, or at the early onset of a pandemic if the strain included in the zoonotic vaccine is still able to cross-protect against the pandemic strain.

Pandemic preparedness vaccines are authorised in advance – before an influenza pandemic– and can be marketed after their composition has been adapted to include the specific virus strain responsible for the outbreak (as identified following the declaration of a PHEIC by the WHO and/or the recognition of a public health emergency at EU level by the Commission). Current regulatory frameworks do not require a formal declaration of a pandemic.

The updated revised vaccines, which are then termed pandemic vaccines, are intended for mass vaccination to protect people against disease caused by the pandemic virus. Based on the authorised technologies and the speed of virus sharing by WHO, it is estimated that pandemic vaccines would become available four to six months after the declaration of a pandemic. Subsequent rapid regulatory approval of the new vaccine antigen by EMA and EC would be facilitated by existing safety data and expedited reviews.

The WHO regularly updates its list of candidate vaccine viruses (CVVs) for zoonotic influenza strains with pandemic potential, based on ongoing global surveillance and genetic, antigenic and epidemiological data.

Some EU Member States vaccinate persons who are occupationally exposed to avian influenza virus outbreaks with seasonal influenza vaccine in order to minimise the risk of reassortment between seasonal and avian influenza strains.

Zoonotic and pandemic preparedness influenza vaccines

Four **pandemic preparedness vaccines** (formerly known as 'mock up' vaccines) are currently authorised in the EU. These can be modified into pandemic influenza vaccines in future pandemics: *Foclivia* (Seqirus), *Adjupanrix* (GSK), pandemic influenza vaccine H5N1 (AstraZeneca) and *Incellipan* (Seqirus) ([33]). As of October 2025, all were still listed as pandemic prototype or 'strain-change'-ready vaccines under EMA supervision, with this regulatory framework allowing antigen updates without a new full authorisation ('strain-change' procedure).

The pipeline for influenza vaccine is increasingly diverse and has incorporated several next-generation strategies. These include (i) broadly protective or 'universal' influenza vaccines aiming to confer cross-clade immunity on human seasonal and potentially pandemic influenza A viruses by targeting conserved viral epitopes; (ii) next-generation vaccine platforms (e.g. mRNA, viral-vector, nanoparticle and nucleic-acid technologies) that offer enhanced adaptability to emergent strains and are being evaluated for influenza in the same way that they have been for other viral pathogens; and (iii) multivalent or combination vaccines that target multiple respiratory pathogens simultaneously (such as influenza, COVID-19 and RS infections).

As of October 2025, these combination vaccines were being developed primarily for seasonal use and not as pandemic or zoonotic vaccines. No authorised or late-stage clinical candidates currently target avian or pandemic influenza strains together with other respiratory pathogens. Universal vaccine candidates (including those targeting conserved regions of haemagglutinin or multiple viral proteins) are currently in Phase II. Many others are in earlier preclinical or Phase I stages use a range of platforms including viral vectors, nanoparticle-based delivery and DNA/RNA technologies.

Three pre-pandemic (zoonotic) influenza vaccines are currently authorised in the EU. All are manufactured by Seqirus. These vaccines are stockpiled for preparedness and are not intended for routine immunisation.

- **Aflunov** is authorised for active immunisation against influenza A(H5N1). The vaccine contains an H5N1 clade 2.2.1 antigen (a lineage that is no longer circulating). The currently circulating H5 viruses belong to clade 2.3.4.4b, so substantial antigenic mismatch is expected and Aflunov is therefore maintained primarily for preparedness and stockpiling purposes (as of October 2025).

- **Celldemic** received marketing authorisation on 19 April 2024. This cell-based vaccine is indicated for the active immunisation of individuals aged 6 months and above against influenza A(H5N1). As of October 2025, the authorised formulation included an H5N1 clade 2.3.2.1c antigen, which predates the currently circulating clade 2.3.4.4b H5 viruses. The vaccine would therefore require an antigenic update before deployment against contemporary H5 strains.

([33]) EMA: Vaccines for pandemic influenza.

- **Zoonotic influenza vaccine** is authorised for use in adults aged 18 years and above. It was granted marketing authorisation on 10 October 2023. Its composition was updated in April 2024 from an H5N1 clade 2.2.1 antigen to an H5N8 clade 2.3.4.4b, in compliance with the WHO and EMA recommendations to match the currently dominant H5 clade 2.3.4.4.b viruses in birds and poultry.

Therapeutics

Several antiviral drugs are available and authorised to treat influenza upon disease onset. Zoonotic influenza are generally susceptible to the same drugs. It is recommended that antivirals should be administered as early as possible because, in later phases of the disease, the host response rather than the direct effects of the virus will increasingly determine the course and outcome of the disease. Alternatively, some antivirals are also approved for pre-exposure prophylaxis (PrEP) in exceptional circumstances (such as when there is a mismatch between the circulating and vaccine virus strains or during a pandemic situation) and for post-exposure prophylaxis (PEP).

Seasonal prevention with oseltamivir may be considered for individuals aged one year or older. The approved labels for influenza antivirals include recommendations for the use of PrEP in exceptional circumstances (for example, if there is a mismatch between circulating and vaccine virus strains) and in a pandemic situation. It can therefore be considered in escalating scenarios where there are human cases in the EU/EEA – especially if there are clusters of cases according to national recommendations for specific groups (e.g. workers involved in culling infected animals), household contacts of confirmed human cases or healthcare workers. It should be noted that prolonged use may have implications for safety or resistance emergence.

PEP with antiviral agents may also be considered for high-risk individuals following close contact with confirmed human or animal cases.

The WHO's clinical guidelines recommend that patients with suspected or confirmed influenza virus infection who present with severe or progressive disease or who are at high risk of complications should receive antiviral treatment as soon as possible. A neuraminidase inhibitor (preferably oseltamivir) should ideally be initiated within 48 hours of symptom onset, but initiation of treatment is still recommended in severe or progressive disease even after 48 hours of symptom onset. Use of other antivirals (e.g. baloxavir marboxil) should follow national guidelines, and should generally be limited to specific indications for seasonal influenza, because evidence for their use in zoonotic or pandemic influenza remains more limited.

Adamantanes (amantadine and rimantadine) inhibit the influenza A M2 ion channel. They were previously used for treatment and prophylaxis of influenza A infections but have now been effectively abandoned because of the near-universal resistance among the currently circulating human influenza A(H1N1)pdm09 and A(H3N2) viruses ([34]). This resistance is primarily mediated by the S31N substitution in the M2 protein.

Resistance to adamantanes is also common in zoonotic influenza viruses, because many avian and swine influenza A strains carry the S31N (and less commonly V27A) substitution in the M2 gene and this confers high-level resistance.

([34]) WHO 2024; ECDC Influenza Antiviral Resistance 2025; CDC 2025.

However, depending on the availability of adamantanes, they may also be considered in line with national recommendations if: (1) other antivirals are not effective against the circulation influenza virus strain or are not available; and (2) it is proven that the circulating zoonotic influenza strain is susceptible to adamantanes.

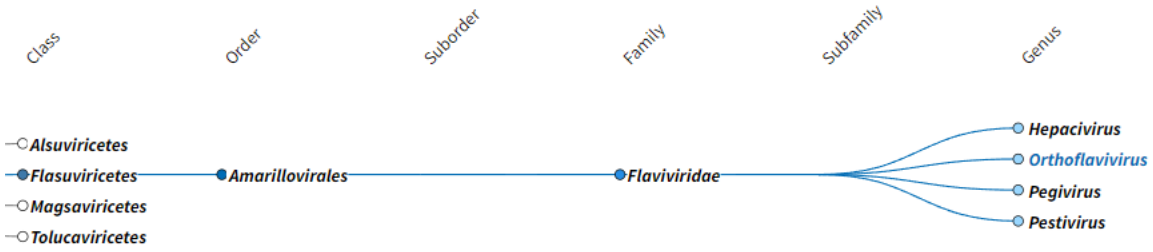
Figure 3. Overview influenza therapeutics

TRADE NAME, MANUFACTURER	ACTIVE PHARMACEUTICAL INGREDIENT (API)	MODE OF ACTION
Tamiflu, Roche	Oseltamivir	Neuraminidase inhibitor, oral administration; authorised for treatment and prophylaxis (PEP and PrEP under exceptional circumstances)
Ebilflumin, Actavis Group	Oseltamivir	Neuraminidase inhibitor, oral administration; authorised for treatment and prophylaxis (PEP and PrEP under exceptional circumstances)
Dectova, GSK	Zanamivir (intravenous)	Neuraminidase inhibitor, intravenous formulation; authorised for treatment of complicated and potentially life-threatening influenza; not authorised for prophylaxis
Relenza, GSK	Zanamivir (inhaled)	Neuraminidase inhibitor; inhalation via diskhaler; authorised for treatment for post-exposure prophylaxis (household PEP); seasonal prophylaxis permitted in some national labels
Xofluza, Roche	Baloxavir marboxil	Cap-dependent endonuclease inhibitor; single-dose oral administration; authorised for treatment of uncomplicated influenza and for post-exposure prophylaxis (age ≥1 year in EU); evidence for use in zoonotic influenza limited
Symmetrel / Mantadix *(national authorisation only)*	Amantadine	M2 ion channel inhibitor; *not active against influenza B; near-universal resistance in circulating A(H1N1)pdm09 and A(H3N2) viruses; not recommended* ([35])
Flumadine *(national authorisation only)*	Rimantadine	M2 ion channel inhibitor; *not active against influenza B; near-universal resistance in circulating A(H1N1)pdm09 and A(H3N2) viruses; not recommended* ([36])

([35]) This is only recommended if other antivirals are not effective against the circulating influenza virus strain or are not available, and if it is proven that the circulating zoonotic influenza strain is susceptible to adamantanes.

([36]) This is only recommended if other antivirals are not effective against the circulating influenza virus strain or are not available, and if it is proven that the circulating zoonotic influenza strain is susceptible to adamantanes.

4.3. *Flaviviridae*



4.3.1. *Main representatives*

Flaviviridae are a family of viruses that include the *Orthoflavivirus* genus (previously classified as flavivirus prior to the 2023 ICTV renaming). Orthoflaviviruses are primarily spread through arthropod vectors, such as mosquitoes and ticks.

Pathogens of interest within this family include:

- dengue virus (DENV; species *Orthoflavivirus dengue*), which the WHO has classified as both a priority and prototype pathogen for the EURO region;
- zika virus (ZIKV; species *Orthoflavivirus zika*) and yellow fever virus (YFV, species *Orthoflavivirus flavi*), which are both priority pathogens at global level;
- West Nile virus (WNV; species *Orthoflavivirus occidentalis*) and tick-borne encephalitis virus (TBEV; species *Orthoflavivirus encephalitidis*), which are both prototype pathogens for the WHO's EURO region.

This family also includes other relevant pathogens which are not currently identified by the WHO as priority or prototype pathogens – notably Japanese encephalitis virus (JEV; species *Orthoflavivirus japonense*), Kyasanur Forest disease virus (KFDV; species *Orthoflavivirus kyasanurense*) and Omsk haemorrhagic fever virus (OHFV; species *Orthoflavivirus omskense*).

The specific vector for each virus varies. DENV, ZIKV, YFV, WNV and JEV are transmitted by mosquitoes (principally *Aedes* spp. for DENV, ZIKV and YFV; *Culex* spp. for WNV; and *Culex tritaeniorhynchus* for JEV). TBEV, OHFV and KFDV are transmitted by ticks (principally *Ixodes ricinus* and *Haemaphysalis spinigera*).

Moreover, some tick and mosquito-borne viruses (including WNV, DENV and ZIKV) can be transmitted from human to human through substances of human origin (SoHo) (i.e. via transfusion of blood and blood components or transplantation of tissues, cells or organs from an infected donor and viraemic donor blood transfusion).

The specific host range for each virus varies. For example, DENV primarily infects humans, while WNV infects a broader range of vertebrate hosts. These include birds (the primary amplifying hosts) and horses. Humans and horses serve as incidental or dead-end hosts.

Table 1: Overview of the main representatives of the Flaviviridae, including vectors and MCM availability in the EU

	WHO prioritisation	Vector (species)	Vector present in EU	Locally acquired (travel-	Vaccine available

				related) cases in 2023	
DENV	Priority pathogen (global & EURO region)	Mosquito (*Aedes* spp.)	Yes	130 (4 900+)	Yes
ZIKV	Priority pathogen (global)	Mosquito (*Aedes* spp.)	Yes	0 (sporadic)	No
YFV	Priority pathogen (global)	Mosquito (*Aedes* spp.)	No	0 (0)	Yes
WNV	Prototype pathogen (EURO region)	Mosquito (*Culex* spp.)	Yes	709 (19)	No
TBEV	Prototype pathogen (EURO region)	Tick (*Ixodes ricinus*)	Yes	3 303 (3 690, *incl. suspected)*	Yes
JEV	*Not prioritised in EU*	Mosquito (*Culex* spp.)	*Not established*	0 (0)	Yes

Aedes mosquito-transmitted *Flaviviridae* viruses:

Dengue viruses (DENV) consist of four closely related serotypes (DENV-1, DENV-2, DENV-3 and DENV-4) which are transmitted to humans through the bite of infected *Aedes* mosquitoes (specifically *Aedes aegypti* and *Aedes albopictus*). These mosquitoes are most active during the day. They breed in standing water, such as in containers, tyres and flowerpots.

Symptoms of dengue fever range from asymptomatic to mild fever to severe and life-threatening forms – including dengue haemorrhagic fever and dengue shock syndrome, which are life-threatening conditions.

Zika virus (ZIKV) is primarily transmitted to humans through the bite of infected *Aedes* mosquitoes. The virus can also be transmitted through sexual contact with an infected person, from mother to child during pregnancy or childbirth. The main mosquito vector for ZIKV is the *Aedes aegypti* mosquito. *Aedes albopictus* is also a competent vector.

ZIKV infections remain asymptomatic in approximately 80% of the cases ([37]) and most people who are infected will recover without any complications. However, some people (particularly pregnant women and their babies) may experience more serious complications. The risk of microcephaly from ZIKV infection is estimated at between 1% and 13% ([38]). Furthermore, current evidence confirms a broader congenital zika syndrome spectrum with neurological, ocular and developmental outcomes becoming detectable months or years after birth.

Yellow fever virus (YFV) is primarily transmitted to humans through the bite of infected *Aedes* mosquitoes. Infections can lead to severe illness (including fever, jaundice and haemorrhagic complications) with a high case fatality rate in severe cases in endemic regions (tropical regions of Africa and South America).

Culex mosquito-transmitted *Flaviviridae* viruses:

West Nile virus (WNV) is primarily transmitted to humans through the bite of an infected mosquito, particularly from the *Culex* genus. *Culex pipiens* is a common vector in urban

([37]) US CDC: Clinical Signs and Symptoms of Zika Virus Disease.
([38]) .

and suburban areas where stagnant water facilitates mosquito breeding, and its preference for feeding on birds sustains the enzootic transmission cycle of the virus.

Most WNV infections cause no symptoms or relatively mild symptoms (e.g. fever, headache, muscle and joint pain, nausea, vomiting, diarrhoea or a rash). WNV can in rare cases lead to severe illness – such as West Nile neuroinvasive disease, which includes encephalitis, meningitis or meningoencephalitis. The overall fatality rate for WNV is about 1%, but the case fatality rate for neuroinvasive disease ranges from 7% to 17%, depending on age and comorbidities ([39]).

Japanese encephalitis virus (JEV) is transmitted to humans through the bite of infected *Culex* mosquitoes. The main mosquito vector for JEV is *Culex tritaeniorhynchus*, which is mainly found in rice paddies, marshes and other areas with standing water.

JEV causes an infection that can result in a range of symptoms, from mild fever and headache to severe encephalitis (inflammation of the brain) and death. The case fatality rate is around 20% to 30% ([40]).

Tick-transmitted *Flaviviridae* viruses:

Tick-borne encephalitis virus (TBEV) is spread by infected ticks of the species *Ixodes ricinus*. This is mainly found in forests, meadows and other areas where there is tall grass and vegetation.

TBEV infections often remain asymptomatic but can sometimes cause tick-borne encephalitis (TBE), involving the central nervous system. The disease typically manifests itself as meningitis, encephalitis or meningoencephalitis. It can also lead to myelitis and spinal paralysis. TBE is a serious and potentially life-threatening disease, with an overall case fatality rate of approximately 1% to 2% ([41]).

4.3.2. Epidemiological situation

The geographic distribution of *Flaviviridae* viruses is diverse. Some viruses (e.g. DENV and YFV) are endemic in some tropical and subtropical regions. Others (e.g. WNV) are found in temperate climates.

The geographic distribution of *Flaviviridae* viruses varies within the EU. DENV is primarily transmitted by *Aedes albopictus* mosquitoes and is primarily confined to southern Europe, particularly the Mediterranean region. West Nile virus is transmitted by Culex mosquitoes and has a broader distribution that encompasses southern, central and eastern Europe. TBEV is transmitted by Ixodes ticks and is endemic in northern and central Europe, with some endemic pockets in western Europe.

DENV is a major public health concern at global level, with an estimated 400 million infections and around 40 000 deaths annually ([42]). However, DENV is not endemic in mainland EU/EEA and most cases are of travellers who have been infected outside this region. Autochthonous (non-travel-associated) DENV cases have nevertheless been

([39]) ECDC West Nile Update 2025.
([40]) WHO JEV Factsheet 2024.
([41]) ECDC TBE Epidemiological Update 2025.
([42]) WHO Dengue Burden Update 2024.

reported in Europe (including in Spain, France, Croatia and Italy) and DENV is endemic in some EU outermost regions like those in the Caribbean.

In 2024, 83 locally transmitted cases were reported in France, 213 in Italy and 8 in the Catalonia region of Spain, between June and October.

Madeira, an autonomous region of Portugal where *Aedes aegypti* is established, experienced a major dengue outbreak in 2012, with more than 2 000 cases reported.

According to the ECDC, the risk of local DENV transmission in mainland EU/EEA outside the vector season (June to October) is low, due to environmental conditions that for the time being appear to remain unfavourable for vector activity and virus replication.

ZIKV has been reported in several EU Member States (including Spain, France, Italy and Portugal). However, nearly all of these cases have been imported by individuals who have travelled there from endemic regions. A single cluster of autochthonous vector-borne transmission that was confirmed in 2019 in the Var *departement* of southern France and involved three locally acquired cases was the first and only documented instance of mosquito-borne ZIKV transmission in continental Europe. In addition, isolated cases of sexual and congenital transmission have been reported in the EU since 2016, but there has been no sustained local circulation of the virus. ZIKV remains non-endemic in the EU/EEA.

YFV is not endemic in the EU/EEA, but there is a risk of imported cases due to international travel. However, it is important to note that vaccination against YFV is mandatory for travellers visiting YFV-endemic countries, because it is often a requirement for entry. This preventive measure significantly reduces the likelihood of YFV importation by returning travellers, making the risk of introducing the virus into the EU/EEA very low.

The geographical range of **WNV** in the EU remains variable. There are notable transmission hotspots in southern and eastern Europe. In 2023, over 700 locally acquired human cases of WNV infection were reported across nine EU Member States. In 2024, WNV activity increased markedly: by the end of the 2024 transmission season, approximately 1 400 locally acquired human cases had been reported in 19 European countries, with Greece, Italy and Romania recording the highest numbers ([43]). The increase is attributed to favourable climatic conditions that support the spread of *Culex* mosquito vectors, as well as to local ecological and urban factors.

As of October 2025, fewer than 10 human cases had been reported for the 2025 transmission season ([44]).

JEV is endemic in parts of Asia, South-East Asia and the Western Pacific. Some sporadic imported cases have been reported in Europe. The primary vector of JEV, *Culex tritaeniorhynchus*, is not established in EU/EEA countries. However, other mosquito species present in Europe (e.g. *Culex pipiens*) have demonstrated potential vector competence under experimental conditions. The current risk of JEV transmission in Europe is low but increasing globalisation and climate change may facilitate the future introduction and establishment of competent vectors and viral circulation. This underscores the need for sustained surveillance and preparedness.

([43]) ECDC West Nile Virus Annual Epidemiological Report 2025.
([44]) ECDC WNV Dashboard 2025.

TBEV is endemic in most countries in central, northern and eastern Europe. The highest incidence of TBEV infection is reported in the Baltic States, Finland and Sweden. It is also prevalent in western Europe (for example, in Austria, Germany and Switzerland). In 2023, the disease caused 3 303 locally acquired cases in the EU/EEA ([45]). Preliminary data from 2024 suggest a continuing upward trend in TBE cases, with some regions reporting infections for the first time. This expansion is apparently due to factors such as climate change, which affects tick habitats and activity periods, and increased human outdoor activities in endemic areas. As of October 2025, TBEV remained a significant vector-borne public health concern in the EU/EEA.

4.3.3. Impact of climate change

Flaviviridae are primarily transmitted by arthropods whose cold-blooded nature makes them highly sensitive to climate change. Climate therefore influences their population density, geographical distribution and the rate of pathogen replication.

Climate change is expanding such arthropods' range northwards and into higher altitudes. Warmer temperatures and longer breeding seasons are increasing vector populations and transmission risks. Altered precipitation patterns (e.g. increased rainfall) are creating more mosquito-breeding habitats. Drought and decreased precipitation may temporarily reduce breeding sites but can also promote vector proliferation when subsequent rains occur.

This shift, alongside globalisation and land-use changes, increases the risk of the introduction – or a shift in the geographical ranges – of some pathogens or vectors in the EU/EEA. Such changes have already been observed for *Aedes albopictus* and *Culex pipiens* populations in southern, central, and increasingly northern Europe ([46]).

Europe has seen autochthonous outbreaks caused by different vectors that have experienced rapid global expansion due to international human mobility and climate change. *Aedes aegypti* is not widely established in Europe, except in parts of Cyprus and Madeira. The mosquito is a highly competent vector for several tropical diseases, including DENV, YFV, chikungunya virus and zika virus. *Aedes aegypti* prefers warm, urban environments but is not restricted to them.

Aedes albopictus (the Asian tiger mosquito) is a moderately competent vector for *Flaviviridae*, is far more ecologically flexible and can be found in suburban, rural, residential and agricultural habitats. The successful spread of *Aedes albopictus* into new regions is driven by its high ecological plasticity, its ability to survive in temperate climates and the facilitation of its dispersal through increased global trade and travel. As of 2025, *Aedes albopictus* was established in at least 20 EU/EEA countries, with confirmed overwintering populations as far north as Germany and the Netherlands. Additionally, studies indicate that climate change exacerbates the risk and spread of *Aedes*-transmitted viruses, because warming temperatures generally expand their habitable range.

Ixodes ticks can transmit the virus that causes several thousand cases of TBE per year in the EU/EEA. The geographic distribution of *Ixodes ricinus* depends strongly on climatic factors such as humidity, soil water and air temperature, as well as on vegetation type, land use and disturbance. Its seasonal activity and geographical range have expanded in terms

([45]) ECDC TBE 2024.
([46]) ECDC 2025; EFSA–ECDC VectorNet 2025.

of both latitude and elevation as a result of the increasing temperatures, which are linked to milder winters and prolonged spring and autumn seasons.

4.3.4. MCM availability

Vaccines

- **DENV.** Two vaccines against DENV have received centralised marketing authorisation in the EU.
    - **Dengvaxia (Sanofi Pasteur)**: this tetravalent chimeric live-attenuated vaccine uses a yellow fever 17D backbone, covering all 4 DENV serotypes. It is authorised in the EU for individuals aged 6-45 years with confirmed prior dengue infection, where it reduces the risk of severe dengue. Its efficacy is influenced by serostatus. However, its global production was discontinued in August 2025, due in part to low global demand and complex post-marketing safety requirements ([47]).
    - **Qdenga (Takeda)**: this live-attenuated tetravalent vaccine was authorised in December 2022 for individuals aged 4 years and older. It is administered in two doses (at 0 and 3 months). Efficacy varies across the four dengue virus serotypes and real-world data on its performance in non-endemic regions such as Europe remain limited. These factors may restrict the widespread implementation of dengue vaccines in an EU outbreak setting. As of October 2025, Qdenga was still available through centralised EU authorisation for both endemic-country use and outbreak stockpiling.

The WHO has identified dengue as a global priority endemic pathogen for vaccine research and development ([48]). Dengue is one of the candidates with high potential for approval by a WHO-listed authority before 2030. Action is required in order to: (i) build awareness of emerging products; (ii) assemble evidence needed for policy decisions; and (iii) establish mechanisms for long-term, equitable access to approved products.

- **ZIKV.** There is currently no licensed vaccine.

- **YFV.** The only available vaccine in the EU is nationally authorised:
    - **Stamaril (Sanofi Pasteur)**: a single-dose live-attenuated vaccine, provides long-term immunity (≥10 years) and is indicated for individuals aged ≥9 months and at risk from endemic exposure travelling to or living in areas where YFV is endemic. Its use in pregnant women and in people older than 60 years of age is based on specific case-by-case considerations because, respectively, it is a live vaccine and persons older than 60 years may be at greater risk of developing serious and potentially fatal adverse reactions (including systemic and neurological reactions (such as neurotropic disease associated with yellow fever vaccine and YEL-AND) and viscerotropic disease associated with yellow fever vaccine (YEL-AVD)) than other age groups.

- **WNV.** There is currently no licensed vaccine.

([47]) https://www.cdc.gov/dengue/vaccine/index.html.
([48]) Hasso-Agopsowicz et al. Identifying WHO global priority endemic pathogens for vaccine research and development (R&D) using multi-criteria decision analysis (MCDA): an objective of the Immunization Agenda 2030. Lancet, 2024.

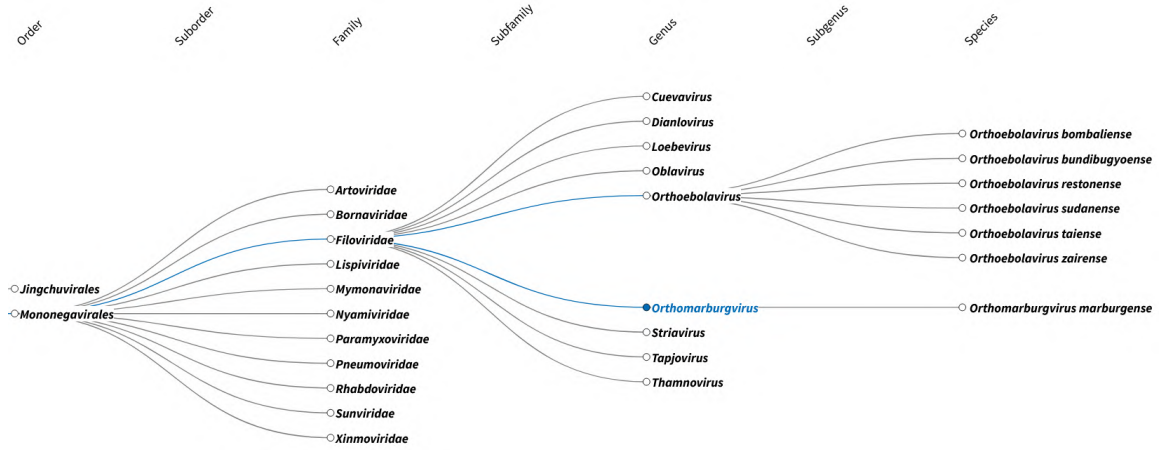
- **JEV.** Only one vaccine has received marketing authorisation, but some inactivated and live-attenuated vaccines also exist in the EU/EEA which target JEV:
  - **Ixiaro (Valneva)** is an inactivated JEV vaccine that is recommended for people aged ≥2 months. It is administered in two doses and a booster is recommended for ongoing exposure.

- **TBEV.** Two licensed TBEV vaccines are currently available in the EU. Both are nationally authorised.
  - **FSME-IMMUN (Pfizer)** and **Encepur (Bavarian Nordic)** are inactivated vaccines that have been authorised in multiple EU Member States where TBE vaccination is indicated, with FSME-IMMUN first licensed in the late 1980s and Encepur in the early 2000s. Both exhibit >95% efficacy and have licensed paediatric dosing and flexible schedules (including rapid and long-term booster).

Therapeutics

There are no approved treatments for DENV, ZIKV, YFV, WNV, JEV or TBEV infections. Treatment remains supportive.

4.4. Filoviridae



4.4.1. Main representatives

The *Filoviridae* family includes nine genera, but only Marburgvirus and ebolavirus are prioritised by institutional threat assessment frameworks due to their high pathogenicity and epidemic potential in humans.

Zaire ebolavirus, Sudan ebolavirus and Marburg marburgvirus are considered priority pathogens. Zaire ebolavirus is considered a prototype pathogen.

Members of the *Filoviridae* family are transmitted to humans primarily through contact with the blood, bodily fluids or tissues of infected animals (e.g. bats or non-human primates) or other infected humans. Transmission may also sometimes occur through exposure to contaminated surfaces or materials such as bedding or medical equipment. The incubation period for filoviruses is typically between 2 and 21 days.

Marburg viruses are responsible for Marburg virus disease (MVD), with a case fatality rate averaging around 50% (ranging from 24% to 90%) depending on virus strain outbreak response and quality of supportive care. MVD is characterised by fever, headache, muscle aches, vomiting, diarrhoea and bleeding. The disease typically begins 5–10 days after exposure to the virus and can progress rapidly, with severe complications such as symptoms of haemorrhagic fever, multiorgan failure, disseminated intravascular coagulation and neurological symptoms.

Ebola viruses cause Ebola virus disease (EVD), another severe and often fatal haemorrhagic fever. The case fatality rate ranges from 25% to 90%, depending on the virus strain, timely diagnosis, and the onset and quality of medical care. EVD is characterised by high fever, headache, muscle aches, vomiting, diarrhoea and bleeding. It typically begins 2–21 days after exposure to the virus and can progress rapidly, with severe complications such as shock, multiorgan failure and disseminated intravascular coagulation.

The ebolavirus genus includes six distinct species. Five of these are known to be pathogenic to humans: Zaire ebolavirus, Sudan ebolavirus, Bundibugyo ebolavirus, Taï Forest ebolavirus and Bombali ebolavirus. All five pathogenic species are found in Africa and cause serious illness in humans. In addition, Reston ebolavirus is found in Asia and can cause epizootics in non-human primates but only causes asymptomatic infection in humans. So far, Reston ebolavirus outbreaks have only been reported in Asia (in China and the Philippines) and have only infected non-human primates and swine.

Ebola virus, which is considered a priority pathogen, has caused the largest and most deadly outbreaks of EVD. These include the 2014–2016 West African outbreak and the 2018–2020 Kivu outbreak.

Not all identified MCM may be effective against all strains. Cuevaviruses and Dianloviruses are closely related to Ebolaviruses and Marburgviruses but are significantly less well-studied and have only been found in a few limited human outbreaks. The Lloviu cuevavirus has been detected in bats in Spain and Hungary. Lloviu virus has repeatedly been associated with bat die-offs (including those in Spain), but its role in causing haemorrhagic disease in bats or potential zoonotic spillover remains unclear.

4.4.2. Epidemiological situation

Globally, as of 4 October 2025, the most recent Filovirus outbreaks had taken place in the following countries.

1. **The Democratic Republic of the Congo (DRC), 2025:** on 4 September 2025, the Minister of Health of the DRC officially declared a new Ebola virus disease outbreak in Kasai Province, affecting the Bulape Health Zone. Laboratory testing at the National Institute for Biomedical Research confirmed the presence of *Orthoebolavirus zairense* (Zaire ebolavirus). As of 28 September 2025, 64 cases (53 confirmed and 11 probable) and 42 deaths (31 confirmed and 11 probable) had been reported, including 5 confirmed healthcare worker cases. Transmission remains confined to six affected health areas within the Bulape Health Zone. Ring vaccination with ERVEBO (rVSV-

ZEBOV) began on 13 September 2025 and is ongoing. The WHO has graded the event as Grade 3 ([49]).

2. **Uganda, 2025**: on 30 January 2025, Uganda's Ministry of Health declared an outbreak of Sudan virus disease following the death of a 32-year-old nurse at Mulago National Referral Hospital in Kampala. As of 7 March 2025, a total of 14 cases (10 confirmed and 4 probable) and 4 deaths (2 confirmed and 2 probable) were reported across the Kampala, Wakiso, Mbale, Jinja and Mukono districts. The outbreak involved two primary clusters: one among family members and one among healthcare workers who had contact with the index case. The last confirmed patient was discharged on 14 March 2025. The outbreak was declared over on 26 April 2025.
3. **Tanzania, 2025**: on 14 January 2025, the WHO announced an outbreak of Marburg virus disease in the Kagera region of northwest Tanzania. The outbreak involved 9 cases and 8 deaths.
4. **Rwanda, 2024**: Rwanda reported its first-ever outbreak of Marburg virus disease in September 2024, with 66 confirmed cases and 15 deaths. The outbreak was declared over in December 2024 after no new cases had been reported for 42 days.
5. **Equatorial Guinea, 2023**: an outbreak of Marburg virus disease was confirmed in February 2023, resulting in 17 confirmed cases and 12 deaths. This was the first time that Marburg virus disease had been detected in Equatorial Guinea.
6. **Tanzania, 2023**: Tanzania reported its first outbreak of Marburg virus disease in March 2023, with 9 cases and 6 deaths. The outbreak was declared over in June 2023.
7. **Uganda, 2022**: Uganda declared an outbreak of Ebola disease caused by the Sudan virus on 20 September 2022. There were 164 total cases (142 confirmed and 22 probable), including 77 deaths and 87 recoveries. The outbreak, which spread across nine districts, was declared over on 11 January 2023.

Filoviruses are primarily found in Africa, but there have been instances of transmission outside the continent – including in the EU.

The likelihood of importation and secondary transmission of *Filoviridae* within the EU/EEA is low because cases are likely to be promptly identified and isolated, and follow-up control measures are likely to be implemented. The West Africa Ebola virus outbreak in 2013–2016 was the largest Ebola virus outbreak to date and caused 28 652 cases and 11 325 deaths across Guinea, Liberia and Sierra Leone. Transmission occurred in large urban centres and hundreds of EU/EEA humanitarian and military personnel were deployed to the affected areas. There were 8 confirmed EVD cases reported in EU/EEA countries in 2014 (7 travel-related and 1 locally acquired in Spain). They were detected during medical evacuations or repatriations to Germany, Norway, Spain and the United Kingdom). In 2015, 1 additional imported EVD case was confirmed in Italy (a healthcare worker returning from Sierra Leone, with no secondary transmission). However, the increase of global travel and trade is increasing the potential for sporadic importation of cases.

4.4.3. Impact of climate change

Climate change is increasingly recognised as a key factor influencing the ecology and epidemiology of *Filoviridae* by altering conditions that affect virus reservoirs,

([49]) WHO AFRO Situation Report DRC/25/03 (28 September 2025); CDC Ebola Situation Summary (updated 28 September 2025); *The Lancet* Correspondence (3 October 2025).

transmission dynamics and human exposure risks. Filoviruses are zoonotic and there is evidence that fruit bats (family of *Pteropodidae*) are natural reservoirs.

Environmental changes associated with climate changes (e.g. rising temperatures, deforestation and altered precipitation patterns) are modifying bat habitats, behaviours and migration patterns, thereby affecting the spatial and temporal dynamics of virus maintenance and spillover risk.

Ecological stressors (e.g. habitat loss or reduced fruit availability during droughts) can induce nutritional stress in bat populations, potentially increasing viral shedding in saliva, urine and faeces. This may increase the likelihood of virus excretion into environments shared with humans or intermediate hosts. Furthermore, bats that relocate in search of food or roosting areas may introduce filoviruses into previously unaffected regions, thereby expanding the geographical risk of outbreaks.

Deforestation and agricultural expansion, which are often driven by climate-induced changes in land productivity, are forcing people into closer contact with bat populations. This is particularly relevant in Central and West Africa, where Ebola virus outbreaks have been linked to increased human activity in forested areas. In addition, climate change is impacting healthcare and outbreak response capacity. More frequent and severe weather events, such as storms and floods, can disrupt healthcare infrastructure and thus make it harder to detect and contain filovirus outbreaks.

4.4.4. MCM availability

Early supportive care is the key to managing filovirus infections. It includes providing fluids and electrolytes, treating co-infections and managing symptoms such as fever, pain, vomiting and diarrhoea. Pathogen-specific MCM are available for some filoviruses.

Vaccines

Three vaccines have received marketing authorisation in the EU/EEA (the second and third being used together).

- **Ervebo** ((rVSV)-ZEBOV-GP; Merck) is a live-attenuated, single-dose recombinant vesicular stomatitis virus (rVSV)-vectored vaccine that expresses the envelope glycoprotein (GP) of the Zaire ebolavirus. It is indicated for individuals aged ≥ 1 year against Zaire ebolavirus. It has demonstrated high efficacy in ring vaccination trials and was first authorised by the EMA in November 2019. The indication was expanded to include children ≥ 12 months in July 2023.

- **Zabdeno** and **Mvabea** heterologous regimen (Janssen-Cilag/Bavarian Nordic):
    - **Mvabea** (MVA-BN-Filo [recombinant]; Janssen-Cilag International NV) contains a virus known as Modified Vaccinia Ankara (MVA), which was engineered by Bavarian Nordic and has been modified to produce four proteins from Zaire ebolavirus and proteins from three other members of *Filoviridae*. It is part of a two-dose vaccine regimen and is administered in combination with Zabdeno (Ad26.ZEBOV-GP). The vaccine has demonstrated effectiveness in preventing EVD caused by the Zaire ebolavirus.
    - **Zabdeno** (Ad26.ZEBOV-GP [recombinant]; Janssen-Cilag International NV) is a recombinant adenovirus type 26 (Ad26) vector-based vaccine that

expresses the glycoprotein of the Zaire ebolavirus Mayinga variant. It is a two-dose vaccine: Zabdeno is given as the first dose and Mvabea is given as the second dose eight weeks later. Zabdeno is effective in preventing EVD caused by the Zaire ebolavirus. The two-dose schedule, requiring an eight-week interval between doses, means that this combination vaccine would only be suitable for pre-exposure prophylaxis outside an outbreak situation.

In 2017, the Chinese National Medical Products Administration (NMPA) approved the application for registration of a recombinant Ebola virus vaccine based on adenovirus technology. The vaccine was developed and produced in China. It uses a recombinant adenovirus type 5 (Ad5) vector, which has been engineered to carry the gene for the glycoprotein (GP) of the Ebola virus, prompting an immune response to protect against Ebola virus infection.

There are currently **no licensed vaccines for Sudan ebolavirus**, but several candidates are under development. In particular, the Sabin Vaccine Institute has initiated Phase 2 clinical trials for its Sudan ebolavirus vaccine in Kenya and Uganda. The International AIDS Vaccine Initiative (IAVI) is (in partnership with Merck and supported by CEPI and BARDA) developing a Sudan virus vaccine candidate (IAVI SUDV-GP), which is based on the VSV platform that is also used in the licensed Zaire ebolavirus vaccine (Ervebo). The US FDA has granted orphan drug designation to Soligenix's SuVax for prevention and post-exposure prophylaxis against Sudan ebolavirus infection.

There are currently **no licensed vaccines for MVD**, but several promising candidates are in various stages of development. The Sabin Vaccine Institute has launched a Phase 2 clinical trial of its Marburg virus vaccine in Kenya and Uganda. The University of Oxford has initiated a first-in-human trial for its ChAdOx1 Marburg vaccine. Sabin's vaccine was also used in the recent Marburg virus disease outbreak in Rwanda, despite not having been included in the planned clinical trials.

There are currently no licensed vaccines for Cuevaviruses and Dianloviruses.

Therapeutics

No marketing authorisation has been granted in the EU for any treatment of filovirus disease, but the US FDA has approved two treatments for Ebola virus:

- **Inmazeb** (REGN-EB3; Regeneron Pharmaceuticals, Inc.) is a combination of three monoclonal antibodies (atoltivimab, maftivimab and odesivimab-ebgn) that bind to the Zaire ebolavirus glycoprotein. They thus block virus infection and induce an antibody-dependent effector function that stimulates the immune cells to target and eliminate infected cells. It is given intravenously over a few hours. Inmazeb was approved by the FDA in October 2020 and is included in the WHO's list of recommended therapeutics for EVD.

- **Ebanga** (Ansuvimab-zykl/mAb114; Ridgeback Biotherapeutics, LP) is a monoclonal antibody that targets the Zaire ebolavirus glycoprotein and is administered as a single intravenous injection. The FDA approved Ebanga in December 2020.

The WHO has issued strong recommendations for the use of Inmazeb and Ebanga in confirmed EVD cases caused by the Zaire ebolavirus, based on clinical trial data that show

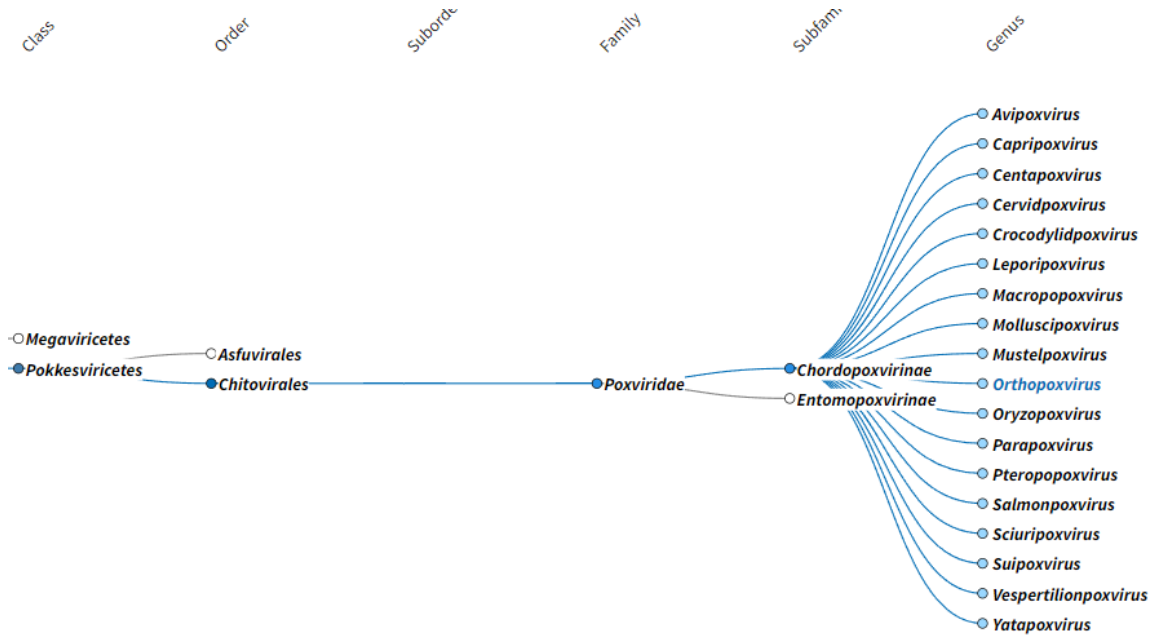
significant reductions in mortality compared with previous standards of care. The WHO emphasises the importance of improving access to these treatments in outbreak scenarios.

There are no licensed therapeutics for Sudan ebolavirus, but several candidates are under development (most notably the monoclonal antibody MBP134 – a cocktail of two broadly neutralising human monoclonal antibodies developed by the Sabin Vaccine Institute and partners, which has demonstrated protective efficacy in preclinical studies against both Ebola and Sudan viruses, Regeneron's SUDV-specific mAb and investigational antivirals like remdesivir). Ongoing efforts are being coordinated through the WHO's R&D Blueprint.

Researchers are investigating the use of monoclonal antibodies for the treatment of MVD. These include MR191-N (a Marburg-specific antibody) as well as Ebola-targeted antibodies such as Inmazeb and Ebanga, which are being explored for their potential against Marburg in preclinical studies. Another promising investigational monoclonal antibody (MPB091) is being studied for its ability to inhibit viral replication.

The WHO has initiated the 'Solidarity Partners' trial using platform-adaptive randomised trial protocols. The aim is to identify effective treatments for filoviruses, including Ebola and Marburg viruses.

4.5. *Poxviridae*



4.5.1. *Main representatives*

Poxviridae are large double-stranded DNA viruses. Infections typically result in the formation of lesions, skin nodules and/or disseminated rash. Members of the *Poxviridae* family exist throughout the world and cause disease in humans and many other types of animals.

Several poxviruses are known to infect humans, causing diseases that range from the relatively mild to the severe. One of the most notorious human poxviruses is variola virus or smallpox virus, which causes smallpox. Smallpox has been eradicated through vaccination programmes, but other poxviruses continue to pose health risks to humans, such as cowpox, molluscum contagiosum virus and *vaccinia* species.

Smallpox is caused by the variola virus and was one of the most devastating infectious diseases in human history, causing widespread outbreaks and significant mortality before its eradication in 1980 through a global vaccination campaign led by the WHO. Smallpox had two forms: variola major (the more severe form) and variola minor (the less common and typically milder form). Smallpox virus was primarily transmitted through respiratory droplets or direct contact with infected individuals or contaminated objects. Smallpox had a high case fatality rate, particularly in unvaccinated populations.

Mpox (formerly known as monkeypox) is caused by the monkeypox virus (MPXV), which the WHO has explicitly identified as a priority pathogen. Mpox presents with symptoms similar to smallpox, including fever, rash and respiratory symptoms. However, the disease is generally less severe, with a much lower case fatality rate. There are two clades of MPXV: clade I and clade II. Clade I causes more severe illness and deaths, reaching up to 10% case fatality in some outbreaks. However, recent outbreaks have had a lower case fatality rate.

Mpox is a zoonotic disease and is prevalent in certain wildlife species (primarily small mammals like rodents) in several central and west African countries. MPXV is transmitted to humans through close contact with infected animals (for example, through bites,

scratches or consumption of bush meat). It can also spread through direct contact with body fluids, lesions or virus-contaminated materials (like bedding).

4.5.2. Epidemiological situation

Mpox Clade IIb remains endemic in West Africa.

In May 2022, several outbreaks of mpox Clade IIb were reported in the EURO region, leading to a rapid escalation of cases. The WHO therefore declared a PHEIC in July 2022. That PHEIC was declared over in May 2023 after a sustained decline in global cases. Transmission was primarily linked to intimate contact (including sexual activity), particularly among men who have sex with men, but the virus itself is not classified as a sexually transmitted infection. According to the ECDC (as of 10 October 2025), more than 25 000 confirmed cases and 10 deaths had been reported in the EU/EEA since the start of the 2022 outbreak.

Mpox Clade I is endemic in Central Africa.

In August 2024, the WHO declared a PHEIC because of the emergence and rapid spread of a new clade of mpox (Clade Ib) in eastern DRC and several neighbouring countries. On 5 September 2025, WHO officially ended the PHEIC status for mpox, stating that cases in affected areas had declined and that sustained emergency status was no longer justified.

The affected countries in this outbreak included Angola, Burundi, the Central African Republic, Congo, Côte d'Ivoire, the Democratic Republic of Congo, Gabon, Guinea, Kenya, Liberia, Morocco, Nigeria, Rwanda, Sierra Leone, South Africa, Uganda, Zambia and Zimbabwe. There were around 20 000 confirmed cases in Africa in 2024. Transmission is primarily driven by close physical contact, including sexual contact. The outbreak has disproportionately affected children and vulnerable populations. There were significant challenges in containment due to limited resources and healthcare infrastructure.

The number of clade I cases in the EU remains low, but 20 cases of clade Ib have been reported since August 2024 (including in Belgium, Germany, France and Sweden), mostly in patients with a positive travel history. All cases were mild, with patients experiencing self-limiting symptoms and no deaths reported, and only limited onward spread was observed. In a few instances, secondary transmission among close household contacts of imported cases. As of October 2025, there was no evidence of sustained community transmission.

4.5.3. Impact of climate change

Climate change may increase the likelihood of *Poxviridae* emergence and transmission via multiple pathways at the human-animal-environment interface. Orthopoxviruses are environmentally stable. For mpox, a viable virus has been recovered from household surfaces for ≥15 days, with greater stability at lower temperatures. Evidence of persistence specifically in soil remains limited. In addition, many poxviruses are zoonotic, with mpox, buffalopox and camelpox being maintained in various wildlife and livestock reservoirs. Climate-driven shifts in animal migration, biodiversity loss and land-use changes (e.g. deforestation and agricultural encroachment) may increase human-animal interfaces and thus increase the likelihood of cross-species transmission. In particular, the large increase in reported mpox cases in 2022–2023 outside endemic regions was driven primarily by sustained human-to-human transmission within specific sexual networks.

Ecological drivers for spillover in endemic settings remain plausible but unproven for these outbreaks.

Livestock-associated poxviruses (e.g. buffalopox and camelpox) may also be influenced by climate-related stress in animal populations (including heat-related immunosuppression and altered grazing or trade patterns), potentially leading to more frequent or geographically expanded outbreaks.

A new dimension of climate-related risk arises from the potential re-emergence of ancient pathogens from thawing permafrost, which may release viable viral particles preserved for centuries. The direct risk to humans remains speculative and low, but the 2016 anthrax outbreak in Siberia, which was probably linked to thawing permafrost and exposed carcasses, has heightened scientific interest in permafrost microbiomes. In this context, the identification of Alaskapox virus, a newly emerging orthopoxvirus in the Alaskan Arctic, has prompted concerns, even though there is no current evidence linking its emergence to permafrost thawing. Its appearance in remote and previously unmonitored regions nevertheless underlines the importance of enhanced surveillance and research into potentially reactivatable pathogens.

4.5.4. MCM availability

Vaccines

Several vaccines are available against smallpox and other orthopoxvirus infections. They are typically classified as first-, second- or third-generation vaccines on the basis of their development platform and safety profile. All **smallpox vaccines** are based on live vaccinia virus. This is a poxvirus that is related to the variola virus, which is the causative agent of smallpox. The vaccinia virus is non-virulent in humans but immunologically cross-protective against smallpox (i.e. it is non-pathogenic in immunocompetent humans but elicits cross-protection).

ACAM2000 is a second-generation smallpox vaccine that contains replication-competent vaccinia virus. It was licensed by the US FDA and has been widely stockpiled globally as a preparedness measure against smallpox.

Third-generation vaccines are based on non-replicating attenuated strains of vaccinia virus. They offer a better safety profile and suitability for immunocompromised individuals. **Imvanex** (Bavarian Nordic) is the only vaccine currently authorised in the EU for prevention of both smallpox and mpox in adults. It is a non-replicating and live-attenuated third-generation vaccine based on the Modified Vaccinia Ankara – Bavarian Nordic (MVA-BN) virus. It is to be administered subcutaneously in a standalone 2-dose treatment.

A comprehensive dataset cannot be generated because smallpox has been eradicated and it is impossible to generate efficacy data. EMA has therefore authorised the vaccine under 'exceptional circumstances'. In September 2024, EMA recommended (and the Commission adopted) a decision to extend the indication for Imvanex to include adolescents aged 12 to 17 years (i.e. Imvanex is now authorised from age 12 upwards).

In the US, the same MVA-BN vaccine is marketed as Jynneos and authorised for prevention of smallpox and mpox in adults (and in younger ages, under the Emergency Use Authorization regime). In Canada, it is marketed as Imvamune and authorised for prevention of smallpox and mpox and related orthopoxviruses.

In 2022, the Commission ensured the availability of the vaccines to respond to the Clade IIb outbreak in the EU by purchasing 330 000 vaccine doses and donating them to EU Member States for immediate response. It also organised joint procurement contracts for vaccines and therapeutics to ensure medium- and longer-term availability.

In 2024, in response to the escalating mpox outbreak in Africa, the Commission (in collaboration with the pharmaceutical company Bavarian Nordic) supplied over 215 000 doses of Imvanex. This was followed by additional donation efforts by EU Member States. These vaccines were distributed to affected African countries based on regional needs and an established vaccination strategy.

Therapeutics

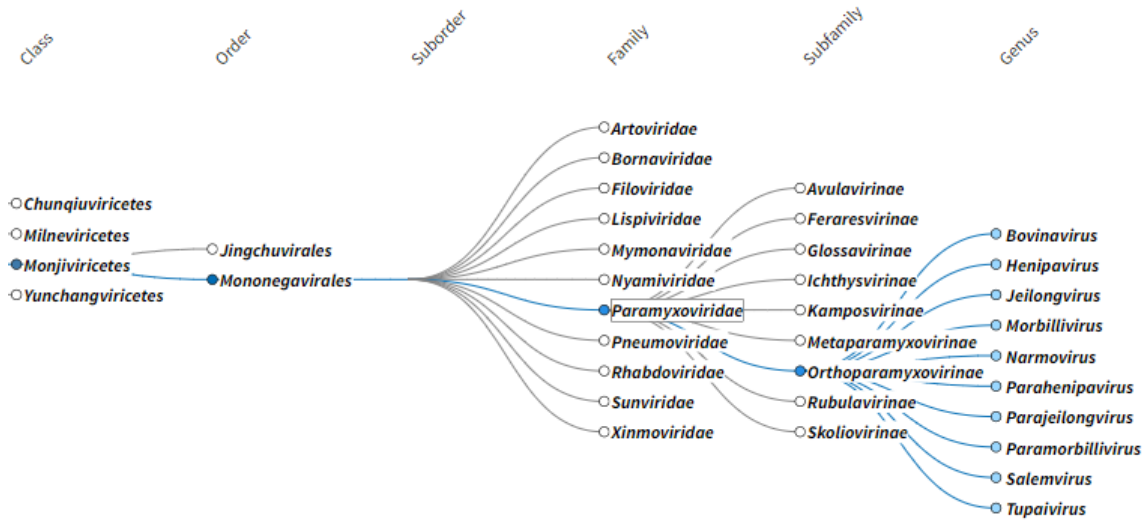
Tecovirimat SIGA (SIGA Technologies Netherlands B.V.) is an antiviral approved by EMA to treat smallpox, mpox and cowpox in adults and children weighing at least 13 kg. Tecovirimat functions by inhibiting the VP37 envelope protein, which is conserved across orthopoxviruses and is essential for the formation and egress of extracellular viral particles. By blocking the interaction between VP37 and host cellular proteins, tecovirimat prevents the development and release of mature virus particles, thereby limiting viral spread within the host.

Tecovirimat was granted marketing authorisation under 'exceptional circumstances' by EMA in January 2022, because traditional human efficacy trials were not feasible due to the eradication of smallpox. Approval was based on robust efficacy data from validated animal models under the FDA Animal Rule, supported by pharmacokinetic and safety data in humans.

However, in late 2024 and early 2025, preliminary results from two clinical trials – PALM007 (carried out in the DRC on patients infected with clade Ib) and the STOMP trial (carried out across multiple sites, primarily in the US, among patients mostly infected with clade II) – failed to show efficacy in reducing disease outcomes (i.e. lesion reduction) or disease severity. Further investigations are ongoing to evaluate Tecovirimat's efficacy.

5. DETAILED DESCRIPTION OF THE GROUP 2 VIRAL FAMILIES: HIGH PRIORITY

5.1. Paramyxoviridae



5.1.1. Main representatives

Paramyxoviridae is a family of viruses that can cause a variety of diseases in humans and animals. Some of the most notable human diseases caused by paramyxoviruses include measles, mumps and parainfluenza. However, this viral family is considered a HERA priority as regards Henipaviruses, a genus within the *Paramyxoviridae* family that includes the Nipah and Hendra viruses.

Henipaviruses can be transmitted to humans through direct contact with infected animals (both wild and domestic). They can cause severe encephalitis in humans and are associated with a high case fatality rate in humans (40-75% for the Nipah virus; up to 60% for the Hendra virus).

Within this family, the **Nipah virus** is considered the priority and prototype pathogen. It is commonly transmitted to humans through exposure to secretions or excretions from infected fruit bats (genus *Pteropus*, family *Pteropodidae*), including consumption of contaminated food such as raw date palm sap, as well as through contact with infected pigs. Human-to-human transmission has also been reported, especially among family members and caregivers that had come into close contact with infected individuals.

The natural reservoir of **Hendra viruses** are flying foxes (*Pteropus* bats). Hendra virus infections in humans are typically associated with contact with infected horses.

5.1.2. Epidemiological situation

The Nipah virus has primarily caused outbreaks in South-East Asia, including Bangladesh, India and Malaysia. Human cases of Nipah virus infection in the EU/EEA have not been documented to date. All known cases since the virus was identified have occurred in Asia.

According to the ECDC ([50]), the most likely route of introduction of the virus into the EU/EEA would be via infected travellers. While importation of the virus through

([50]) ECDC: Communicable Disease Threats Report. Week 38, 17 - 23 September 2023.

agricultural trade, such as live animals or animal products, cannot be excluded, is currently considered very unlikely. Even if a case were to be imported, the likelihood of the virus spreading within the EU/EEA would still be very low. The natural reservoir host of Nipah virus – fruit bats of the *Pteropodidae* species – is not native to Europe.

To date, no cases of Hendra virus infection have been reported in the EU. The virus is mainly found in Australia, where sporadic outbreaks have occurred in horses and only a few cases of human infection have been reported.

5.1.3. Impact of climate change

Climate change is influencing the Nipah and Hendra viruses by altering bat ecology, increasing spillover events and expanding transmission risks.

Globally for the Nipah virus, rising temperatures and habitat destruction are pushing *Pteropus* fruit bats closer to human settlements, increasing the risk of viral spillover through contaminated food (e.g. date palm sap) and direct contact with infected animals. Extreme weather events (e.g. droughts and cyclones) disrupt bat migration, leading to outbreaks in new regions.

For Hendra virus, warmer temperatures and altered flowering and fruiting patterns of trees influence bat feeding behaviour and result in them coming into increasing contact with horses, which serve as intermediate hosts. More frequent rainfall and flooding may also heighten viral transmission by contaminating water sources with bat excreta.

5.1.4. MCM availability

Vaccines

There is currently no licensed vaccine for the Nipah virus or the Hendra virus in humans. Several vaccine candidates are in early clinical development. These include (i) the HeV-sG-V, a recombinant subunit vaccine that targets both Hendra and Nipah viruses; (ii) Moderna's mRNA-1215, an mRNA vaccine which encodes the Nipah virus attachment glycoprotein; and (iii) University of Oxford's ChAdOx1 NipahB, a viral-vector vaccine based on the ChAdOx1 platform. In addition, (iv) PHV02, a recombinant VSV-based vaccine expressing glycoproteins from Ebola and Nipah viruses, has been described in preclinical development, although, as of October 2025, no confirmed public record indicates progression to a human Phase 1 clinical trial.

A veterinary vaccine against Hendra (a subunit-adjuvanted vaccine that contains recombinant Hendra virus G glycoprotein) produced by Zoetis was approved in Australia in 2015 for the protection of horses against Hendra virus infection ([51]).

([51]) Halpin et al. Sero-Monitoring of Horses Demonstrates the Equivac HeV Hendra Virus Vaccine to Be Highly Effective in Inducing Neutralising Antibody Titres. Vaccines (Basel). 2021 Jul 2;9(7):731. doi: 10.3390/vaccines9070731

Therapeutics

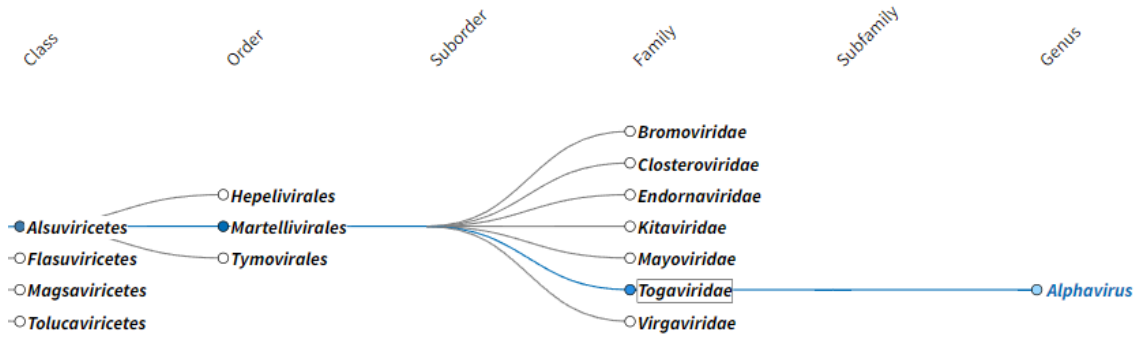
There are currently no approved antiviral treatments for Hendra or Nipah virus infections in humans. Treatment is primarily supportive and often involves measures to manage symptoms such as fever, respiratory distress and neurological complications.

Off-label use of ribavirin has been attempted for Hendra and Nipah viruses in laboratory settings, but its efficacy in humans remains to be demonstrated.

Remdesivir has shown efficacy in non-human primate models of the Nipah virus when administered soon after infection, but there is no confirmed evidence of clinical benefit in humans.

The monoclonal antibody m102.4, which has completed Phase 1 clinical trials, has been used for compassionate use during outbreaks. However, clinical evidence supporting the use of remdesivir or m102.4 in humans is very limited and remains investigational.

5.2. *Togaviridae*



5.2.1. Main representatives

The *Togaviridae* family comprises the genus Alphavirus, whose members are primarily transmitted by mosquitoes and can cause a variety of diseases in humans and animals. The chikungunya (CHIK) and Venezuelan equine encephalitis (VEE) viruses are the two priority and prototype pathogens within this family. The family also includes other pathogens – the Western equine encephalitis (WEE) and Eastern equine encephalitis (EEE) viruses.

5.2.2. Epidemiological situation

Chikungunya virus (CHIKV) is primarily transmitted to people through the bite of infected mosquitoes (mainly *Aedes aegypti* and *Aedes albopictus*). The most common symptoms of the infection are fever and severe joint pain. Polyarthritis can become chronic and disabling. Severe symptoms and deaths from chikungunya are rare and usually related to other coexisting health problems.

CHIKV is not considered endemic in mainland Europe but has caused autochthonous outbreaks in recent years, including in France and Italy. According to the ECDC ([52]), approximately 620 000 chikungunya cases and 213 CHIKV-related deaths were reported in 23 countries and territories in the Americas, Africa, Asia and Europe during 2024.

As of mid-2025 (data to ~August), roughly 317 000 cases and 135 deaths had been reported in 16 countries and territories worldwide for the 12-month period up to August (September 2024 to August 2025). In the French overseas territories (not continental Europe), the situation remains significant. For example, Réunion has reported more than 54 550 autochthonous cases of CHIKV (as of 10 August 2025) in the current season. In Mayotte, more than 1 200 autochthonous cases have been documented to date.

Onward transmission of CHIKV in the mainland EU/EEA requires introduction by viraemic travellers into areas with established competent vectors (e.g. *Aedes albopictus* and *Aedes aegypti*).

Venezuelan equine encephalitis virus (VEEV) can affect equids and humans. The vectors for human transmission are the *Culex tarsalis*, *Culiseta* and *Aedes* mosquito

([52]) ECDC: Chikungunya virus disease worldwide overview (https://www.ecdc.europa.eu/en/chikungunya-monthly).

species. *Aedes aegypti* has been suggested as a potential vector of Venezuelan Equine Encephalitis virus ([53]). Infections in humans are associated with varying degrees of severity depending on the specific VEEV strain. In humans, VEE is usually an acute, often mild, systemic illness ([54]). However, in up to 14% of the cases, the disease can develop into a serious encephalitic disease and long-lasting neurological disease. Infected children are more likely than adults to develop lasting neurological sequelae and fatal encephalitis. Pregnant women infected with VEEV are at risk of congenital disabilities, spontaneous abortions, preterm deliveries and stillbirths ([55]).

VEEV is not present in the EU. Outbreaks of VEEV in humans and equids have been reported in at least 12 countries, including Colombia, Costa Rica, Ecuador, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama, Peru, the US and Venezuela. In 1995, both Colombia and Venezuela reported outbreaks involving an estimated 100 000 human cases. 3 000 of these experienced neurologic complications and there were 300 associated deaths. Only one human case has been documented since 1998.

Western equine encephalitis virus (WEEV) and **Eastern equine encephalitis virus (EEEV)** are arboviruses primarily transmitted by mosquitoes. Birds are the main reservoir hosts. They can cause severe neurological disease in humans, horses and certain bird species. To date, no outbreaks of EEV or WEEV have been recorded in Europe, but suitable environmental and trade-related conditions conditions could, under certain circumstances, facilitate future introduction.

5.2.3. Impact of climate change

The primary vectors of CHIKV are mosquitoes from the *Aedes aegypti* and *Aedes albopictus* species. *Aedes albopictus* is established in a large part of Europe, including France, Italy and the Balkan region. *Aedes aegypti* is established in Cyprus, on the eastern shores of the Black Sea, in Madeira and in other outermost regions.

Climate change is facilitating the geographic expansion of *Aedes* mosquitoes by increasing average temperatures, lengthening breeding seasons and creating favourable humidity and precipitation conditions. As ectothermic (cold-blooded) organisms, mosquitoes are particularly sensitive to temperature changes, which affect not only their population density but the virus replication rates, thereby reducing the extrinsic incubation period and increasing transmission potential.

In the case of Venezuelan equine encephalitis virus (VEEV), transmission typically involves the *Culex* and *Aedes* mosquito species, many of which are not currently present in the EU. The vector competence of European *Culex* and *Aedes* species for VEEV remains poorly analysed, so there is uncertainty in assessing potential transmission risk under climate change scenarios. However, if suitable vectors become established or imported, the risk of VEEV emergence in Europe may increase under warming conditions.

Overall, climate-driven ecological shifts (including the expansion of vector habitats, increased frequency of extreme weather events and changing land-use patterns) are

([53]) ECDC: Increasing risk of mosquito-borne diseases in EU/EEA following spread of Aedes species. June 2023.
([54]) Centre for Food Security & Public Health: Eastern, Western and Venezuelan Equine Encephalomyelitis.
([55]) https://www.ncbi.nlm.nih.gov/books/NBK559332/.

expected to enhance the risk of local CHIKV outbreaks and potentially introduce other vector-borne togaviruses into previously unaffected areas of the EU/EEA.

5.2.4. MCM availability

Vaccines

Two **chikungunya vaccines** are authorised in the EU.

- Vimkunya (Bavarian Nordic) is a single-dose virus-like particle (recombinant, non-replicating) vaccine. It received marketing authorisation on 28 February 2025 for the prevention of CHIKV disease in individuals aged 12 years and older (single dose, attenuated vaccine).

- Ixchiq (Valneva) is a single-dose live-attenuated vaccine. It was authorised on 1 July 2024 for the prevention of CHIKV disease in adults. EMA temporarily suspended its use in persons aged ≥ 65 years in May 2025 pending a safety review (following reports of serious adverse events in older people), but in July 2025 lifted that age restriction after assessment by PRAC. In August 2025, the US FDA's Center for Biologics Evaluation and Research suspended the biologics licence for the Valneva Ixchiq vaccine in the US.

The Commission is, in partnership with CEPI, supporting late-stage clinical trials to facilitate regulatory approvals of the vaccine for adolescents and ensure affordable access to the vaccine in endemic regions ([56]).

No authorised human vaccine exists within the EU for EEE and VEE. Experimental human vaccines against EEEV and VEEV (e.g. the US Army's inactivated EEEV vaccine and the live-attenuated TC-83 VEEV strain) are not licensed for general use and are only available under US military IND protocols. Neither vaccine is approved for human use in the EU, but TC-83 remains in limited veterinary use for horses in endemic regions.

Vaccines are also available for horses in EEEV-endemic and VEEV-endemic regions.

Therapeutics

No specific treatment exists fo

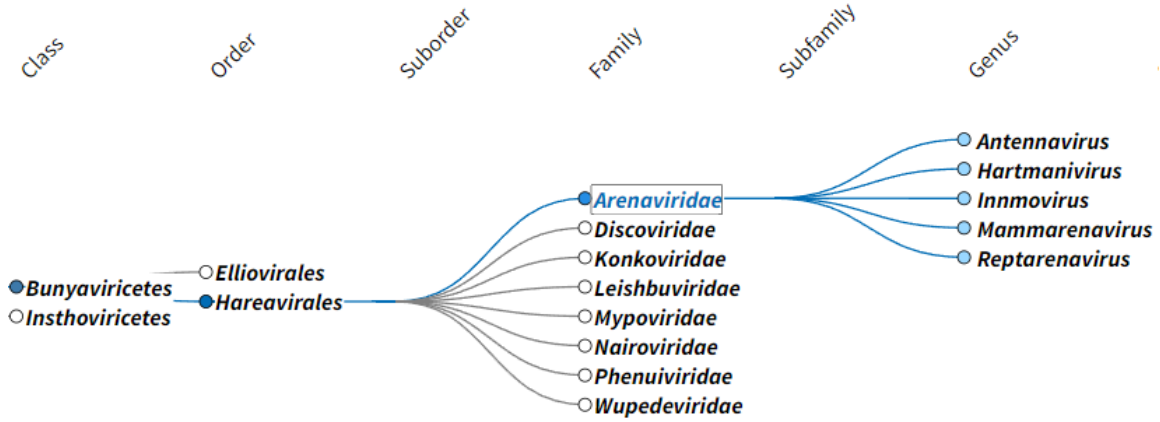
r CHIKV, VEEV, EEEV or WEEV infections. Supportive care is the primary approach.

Severe forms of EEEV and VEEV infection may require intensive care, including airway protection, sedation and intracranial pressure management. Long-term neurological sequelae are common in survivors of EEEV neuroinvasive disease.

In the case of CHIKV, prolonged post-infectious arthralgia may require anti-inflammatory therapy, corticosteroids or specialist rheumatological management in chronic cases.

([56]) CEPI expands partnership with Valneva with $41.3 million to support broader access to world's first Chikungunya vaccine. July 2024

5.3. *Arenaviridae*



5.3.1. *Main representative*

Arenaviridae are a family of zoonotic RNA viruses that cause a variety of diseases in humans and animals. They are generally transmitted by rodents. Each virus is associated with one (or a few) closely related rodent species that serve as the virus's natural reservoir and that are located across most of the world (including Europe, Asia, Africa and the Americas). Highly pathogenic arenaviruses are not endemic to the EU/EEA, but imported cases (particularly of Lassa fever) have been reported in travellers returning from endemic regions in Africa.

Mammarenaviruses are the genus of interest among *Arenaviridae*. Mammarenaviruses can be divided into two groups, based on genetic differences and geographical distribution. **New World** arenaviruses are found in the Western Hemisphere (i.e. North and South America). They include the species *Chapare mammarenavirus* and *Machupo mammarenavirus* viruses (to be found in Bolivia), *Guanarito mammarenavirus* (to be found in Venezuela), *Sabia mammarenavirus* (to be found in Brazil and synonymously called Brazilian mammarenavirus – BzHF) and *Junin mammarenavirus* (JUNV) (to be found in Argentina). **Old World** arenaviruses occur in the Eastern Hemisphere (i.e. Africa, Europe and Asia). Lassa mammarenavirus (LASV), which can cause mild to severe disease in people, is found in western Africa, while Lujo mammarenavirus (LUJV) is found in southern Africa.

Priority pathogens within this family include the Lassa virus (which also serves as the prototype pathogen), as well as the Lujo and Junin viruses.

Transmission occurs via contact with shed viruses in the urine, saliva, droppings or nesting materials of infected rodents, through bites or scratches by infected rodents, and by eating rodent-contaminated food. In a few instances, arenaviruses have been transmitted to humans when infected rodents were eaten.

Person-to-person transmission by direct contact with blood or other body fluids of infected individuals has been reported for certain arenaviruses, such as the Chapare, Lassa, Machupo and Lujo viruses. Contact with contaminated objects (e.g. medical equipment) is associated with transmission. All arenaviruses affecting humans are known to cause haemorrhagic fevers and are of particular concern due to their high case fatality rates and potential for localised outbreaks.

The most frequently occurring and best-studied member of the *Arenaviridae* is Lassa mammarenavirus (LASV), the causative agent of Lassa fever. It is endemic in parts of West Africa (e.g. Guinea, Liberia, Nigeria and Sierra Leone). Neighbouring countries are also at risk of LASV infections due to the widespread presence of its animal reservoir, the common African rat (*Mastomys natalensis*). About 100 000–300 000 infections of Lassa fever occur annually, with about 5 000 deaths. Variations in surveillance for LASV between regions leads to crude estimates. Diagnostic challenges and limited seroprevalence studies also make it more complicated to obtain accurate exposure rates. In some areas of Liberia and Sierra Leone, Lassa fever accounts for about 10-16% of annual admissions to hospital.

5.3.2. Epidemiological situation

Arenaviridae infections are not endemic in the EU and imported human cases remain very rare. However, there is a risk of cases being imported to EU/EEA from endemic regions such as West Africa and South America.

An ECDC rapid risk assessment published in November 2019 assessed the likelihood of the general population encountering a Lassa fever case in the EU/EEA as very low. Transmission of Lassa virus from travel-associated or air-lifted cases is rare. In addition, the principal animal reservoir (*Mastomys natalenis*) is not native to Europe.

5.3.3. Impact of climate change

Climate change is increasingly influencing the ecology and epidemiology of *Arenaviridae.* Rising temperatures, altered precipitation patterns and habitat fragmentation are driving changes in rodent populations that serve as natural reservoirs for these viruses, potentially expanding their geographical range and thereby increasing the likelihood of human exposure.

For instance, shifting climate conditions could push rodent hosts of Machupo and Chapare viruses into new areas of Bolivia, altering transmission dynamics. Similarly, the habitat of *Calomys spp.* (the primary reservoir for Junin virus) may expand in response to environmental changes, increasing the risk of Argentine haemorrhagic fever. Extreme weather events (such as floods in Brazil and Venezuela) can also displace rodent populations, forcing them into closer contact with human settlements and thereby facilitating the spread of Guanarito and Sabia viruses. Additionally, prolonged droughts and food shortages may lead to increased human consumption of rodents as a food source in some endemic regions, exacerbating the risk of direct transmission.

The evolving climate landscape underscores the urgent need for enhanced surveillance, ecological studies and public health preparedness to mitigate the potential for arenavirus outbreaks in a changing world.

5.3.4. MCM availability

Vaccines

Several vaccine candidates are being investigated, but no vaccines are currently authorised in the EU. Several candidate vaccines are under development against Lassa fever and Argentine haemorrhagic fever (caused by Junin virus). In February 2025, rVSVΔG-LASV-GPC became the first Lassa fever vaccine candidate to receive PRIME designation from EMA. This designation is intended to expedite the development of medicines that address unmet medical needs, particularly those that show early clinical

promise. The WHO and CEPI have prioritised vaccine development against Lassa infection and several candidates in preclinical and clinical development exist. Candid#1, a live-attenuated Junin virus vaccine is only licensed in Argentina.

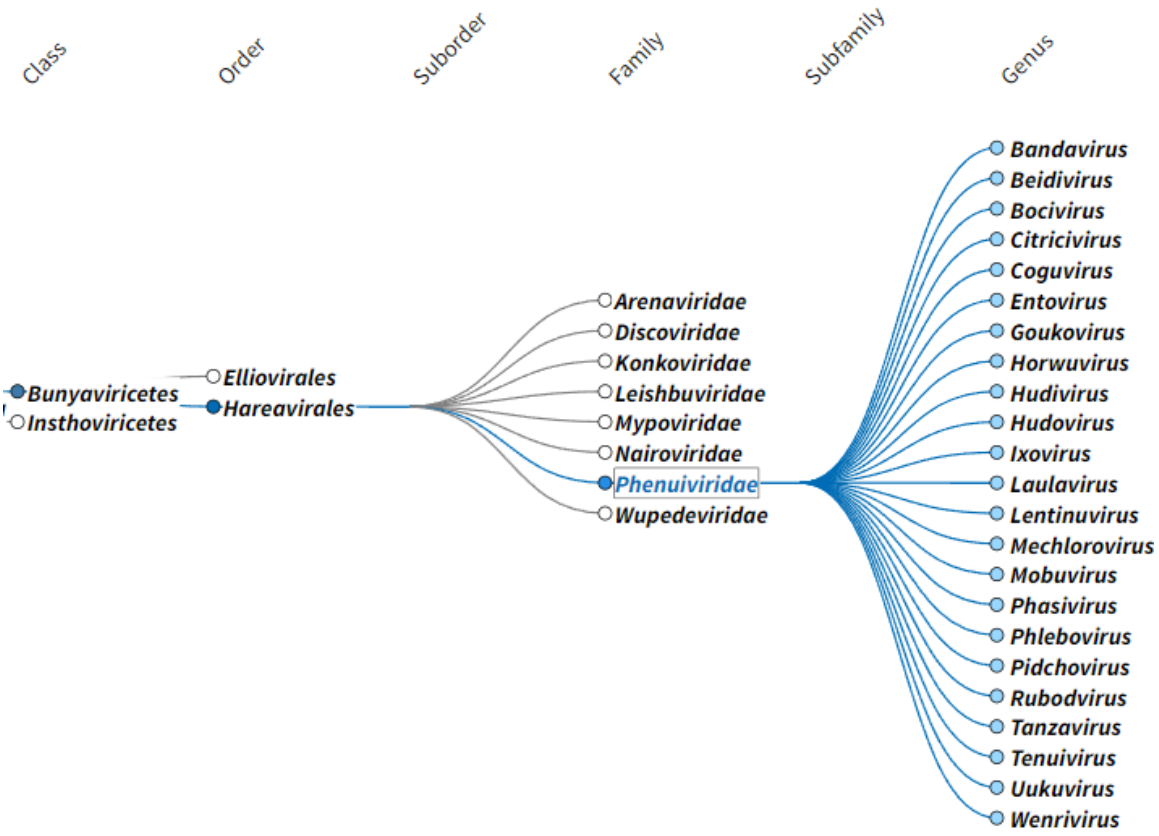
There are no specific vaccines available for Chapare, Guanarito, Lujo, Machupo and Sabia arenavirus infections.

Therapeutics

There are currently no therapeutics authorised in the EU for *Arenaviridae*, but several options are under development. These include repurposed medicinal products and other products undergoing clinical development for both Lassa and Junin virus infections.

There are no specific treatments authorised in the EU for Chapare, Guanarito, Lujo, Junin, Machupo or Sabia mammarenavirus infections.

5.4. *Phenuiviridae*



5.4.1. *Main representatives*

Phenuiviridae includes several genera and species that are significant pathogens for humans, animals and plants. They are primarily transmitted by arthropod vectors such as mosquitoes, ticks and sandflies.

Priority pathogens include **Rift Valley fever virus (RVFV)** (genus Phlebovirus), which affects livestock and humans, and **Dabie bandavirus**, formerly named **severe fever with thrombocytopenia syndrome virus** (**SFTSV**).

RVF is a mosquito-borne viral disease that can affect cattle, sheep, camels, goats and humans. Recovery is complete in uncomplicated cases. In rare cases (fewer than 1%), Rift Valley fever progresses to ocular disorders, meningoencephalitis or a haemorrhagic form (the haemorrhagic form has a 50% case fatality rate). Extensive clusters of abortions may develop in livestock before human cases appear. Animal herdsmen, slaughterhouse employees, butchers, laboratory personnel and veterinarians are among the main risk groups in humans, because the disease is mainly contracted by handling the blood and tissues of infected – dead or alive – animals.

Human infections have also resulted from the bites of infected mosquitoes. The virus is transmitted via mosquito bites of the *Aedes* and *Culex* types, which can transmit the virus to their offspring through eggs where the virus can persist from months to years. The transmission can amplify in naïve ruminants via local competent mosquitoes like *Culex, Mansonia* and *Anopheles* that act as mechanical vectors.

SFTS is a tick-borne viral disease associated with acute fever, possibly accompanied by vomiting, diarrhoea, fatigue, myalgia and leukocytopenia. The fatality rate is about

5-15% ([57]). Most reports of infection have come from studies in China, Japan and South Korea, but Myanmar, Taiwan and Vietnam have also had confirmed cases in recent years ([58]). Severe infections can cause haemorrhagic fever and multiple organ failure leading to death. In Thailand, the high frequency of arboviral infections (primarily dengue and chikungunya) often complicates the diagnosis of febrile illnesses caused by other viruses (such as SFTSV) due to limited clinician awareness.

5.4.2. Epidemiological situation

RVF is endemic in sub-Saharan Africa and the Arabian Peninsula and has periodically caused outbreaks in these regions. During the last two decades, over 4 000 cases and ~1 000 deaths have been reported ([59]).

An outbreak of RVF occurred in 2019 in Mayotte, causing more than 80 human cases.

According to the European Food Safety Authority (EFSA), the movement of infected animals and vectors remains a possible pathway for the introduction of the virus to the EU, but the overall risk of RVFV being introduced through the animal pathway is very low for all EU Member States. Similarly, the risk of introduction through the vector pathway is also very low for most EU Member States. Various mosquito species (particularly *Aedes* and *Culex* spp.) can transmit RVFV and the actual species involved can vary depending on the region. *Culex pipiens*, a widely distributed mosquito species in Europe, has shown a high level of vector competence for the transmission of RVFV.

Since the initial identification of the SFTSV in ticks in rural areas of China in 2009, the virus has been increasingly isolated from a diverse array of hosts around the world, thus demonstrating a rising trend in incidence. Between 2011 and 2021, about 20 000 cases were confirmed in China, mainly in the central regions of the country. Japan has reported SFTS cases since 2013, with nearly 1 000 confirmed cases as of 2024, including approximately 100 fatalities (a case fatality rate of around 10%). South Korea also reported over 2 000 confirmed cases and around 380 deaths reported between 2013 through 2024 ([60]) has also had SFTS cases since 2013.

The main vector of the virus, the tick species *Haemaphysalis longicornis*, is native to eastern Asia but has recently reached the USA. This species is common in the world but has never been reported in Europe. Predictive modelling suggests that it could become established Europe given the right climatic conditions ([61]).

5.4.3. Impact of climate change

Vector-borne transmission of *Phenuiviridae* viruses (notably RVFV) is highly sensitive to environmental and climatic conditions. Warmer temperatures, altered rainfall patterns and

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([57]) Taiwan Centers for Disease Control: Severe Fever with Thrombocytopenia Syndrome.

([58]) Emerging Infectious Diseases, Volume 28, Number 12—December 2022: Severe Fever with Thrombocytopenia Syndrome Virus Infection, Thailand, 2019–2020.

([59]) Petrova et al. Rift valley fever: diagnostic challenges and investment needs for vaccine development. BMJ Global Health. August 2020.

([60]) Korea Disease Control and Prevention Agency: Surveillance of Tick Populations in the Republic of Korea in 2024

([61]) Zhao et al. Distribution of Haemaphysalis longicornis and associated pathogens: analysis of pooled data from a China field survey and global published data. August 2020. 10.1016/S2542-5196(20)30145-5

extreme weather events create favourable conditions for mosquito populations capable of carrying RVF, such as the *Aedes* and *Culex* species. This allows these vectors to expand into new regions and increases the potential for virus transmission. Heavy rainfall and flooding lead to large-scale hatching events, significantly increasing mosquito density, and increase the likelihood of RVF outbreaks. As these conditions become more frequent, vector populations are expanding into new geographic areas, heightening the risk of virus transmission and complicating vector control efforts.

Movement of infected animals: strict EU regulations limit the risk of RVFV introduction through formal livestock trade, but climate-driven droughts and floods in endemic regions can force the movement of infected animals into new areas where competent vectors are present. This raises concerns about spillover events and localised transmission.

5.4.4. MCM availability

Vaccines

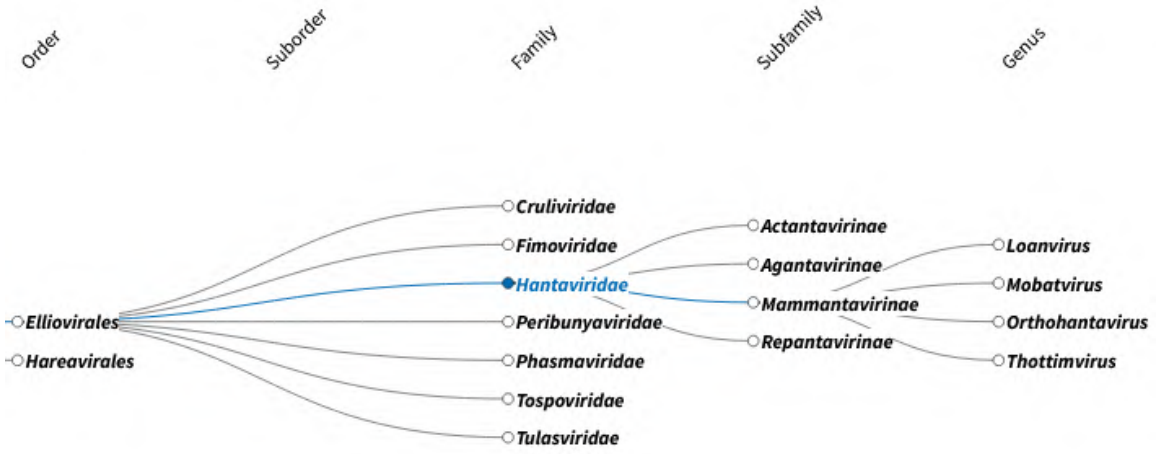
Vaccines for RVF (including the live-attenuated *Smithburn* vaccine and various inactivated formulations) are currently available for veterinary use but are not widely distributed on a global scale. No human vaccines have received regulatory approval to date, but significant efforts are underway to advance human vaccine candidates, and several of these are in the late preclinical or early clinical development stages.

No licensed vaccines for SFTSV are available for either human or veterinary use. Despite the virus's high case fatality rate and increasing geographic spread, vaccine development remains in the early stages and most candidates are still in preclinical evaluation. A limited number of human vaccine candidates have entered early-phase clinical trials and intensified efforts are underway (particularly in East Asia) to accelerate development in response to rising public health concerns. A vaccine developed by Oxford University similar to the COVID-19 vaccine is undergoing Phase II clinical trials. CEPI is supporting this vaccine and two others (including an mRNA vaccine) through development.

Therapeutics

No antiviral treatments are currently approved for the treatment of RVF. Off-label use of RNA-dependent RNA polymerase inhibitor antivirals like ribavirin and favipiravir are under investigation and may, depending on the results, demonstrate potential for future clinical trials investigations.

5.5. Hantaviridae



5.5.1. Main representatives

Hantaviridae is a family of viruses primarily transmitted to humans via rodents. These viruses can cause severe human diseases, such as haemorrhagic fever with renal syndrome (HFRS) and hantavirus cardiopulmonary syndrome (HCPS). HFRS is prevalent in Europe and Asia, while HCPS is more common in the Americas. HCPS has not been reported in Eurasia.

The priority pathogens among the *Old World* orthohantaviruses are the Hantaan virus and the Sin Nombre virus (also a prototype pathogen).

The **Hantaan orthohantavirus (HTNV)** is responsible for most HFRS cases worldwide and is primarily found in Asia. There is only sporadic transmission of HTNV in the EU (mostly in Greece).

The **Sin Nombre orthohantavirus (SIOV)** causes HCPS, which is a severe and often fatal disease that is endemic in North America.

Other pathogens in this viral family, which the WHO has not identified as priority or prototype pathogens, include:

- the **Puumala orthohantavirus (PUUV)**, which can cause nephropathia epidemica (a mild form of HFRS) characterised by fever, renal impairment and sometimes haemorrhagic manifestations ;
- the **Dobrava-Belgrade orthohantavirus (DOBV)**, which causes HFRS. It is found in south-eastern and central Europe (including Croatia, Slovenia and the Balkans) and causes a more severe form of HFRS with a higher fatality rate;
- the **Seoul orthohantavirus (SEOV)**, which is primarily found in Asia, with only sporadic transmission in the EU. It causes a milder form of HFRS than HTNV and DOBV;
- the **Andes orthohantavirus (ANDV)**, which causes Andes haemorrhagic fever (AHF), a serious but rarely fatal disease endemic in South America. No cases of AHF have been reported in the EU;

- the **Choclo orthohantavirus (CHOV)**, which is a hantavirus closely related to ANDV. CHOV has been isolated from rodents in Argentina, but its role in human disease is unknown. No cases of CHCV have been reported in the EU;
- the **Laguna Negra orthohantavirus (LANV)**, which is a hantavirus closely related to SEOV. LANV has been isolated from rodents in Argentina, but its role in human disease is unknown. No cases of LANV have been reported in the EU.

5.5.2. Epidemiological situation

Hantaviruses are typically transmitted through inhalation of aerosolised virus particles from rodent excreta, such as urine, faeces and saliva. In Europe, certain rodent species serve as *Hantaviridae* reservoirs.The incidence of hantavirus infections in Europe vary geographically, with northern and central regions reporting higher incidences. According to the latest ECDC report published on hantaviruses in January 2023 (for 2020), 28 countries reported 1 647 cases of hantavirus infection (0.4 cases per 100 000 population), mainly caused by Puumala orthohantavirus (PUUV) (98%) and primarily in northern and central Europe (including Belgium, Germany, France, Finland and Sweden). During 2016 to 2020, the overall notification rate fluctuated between 0.4 and 1.0 cases per 100 000 population ([62]). Then, in 2020, two countries (Germany and Finland) accounted for 85% of all reported cases, with Finland alone accounting for 71% of all cases.

In 2020, HTNV was identified in 14 cases (13 in Slovakia and 1 in Slovenia) and DOBV in 7 cases, predominantly reported from Central and Southeastern European Member States.

A few cases of HPS have been reported in Europe, but it is not known whether these cases were caused by SIOV. Since 1993, the annual reported cases of SIOV in the United States have consistently ranged between 10 and 50 cases per year, accounting for approximately 850 reported cases across 39 states to date ([63]). Distribution of the virus is primarily due to the geographic range of the deer mice that serve as the primary carriers of SIOV.

According to the ECDC ([64]), Hantavirus infections are underdiagnosed in many regions in Europe. The respective role of different rodent species in transmitting rodent-borne diseases needs to be further assessed. Rodent vector control strategies need to be further developed.

5.5.3. Impact of climate change

Climate change is significantly influencing the dynamics of *Hantaviridae* by altering environmental and ecological conditions that affect rodent populations and virus transmission. Warmer temperatures and milder winters contribute to higher rodent survival rates, leading to increased population densities. Rising temperatures extend the breeding season, allowing rodents to reproduce more frequently and to move into new areas, thereby potentially introducing hantaviruses to regions where they were previously absent. Rodents in search of food and shelter are increasingly encroaching on human settlements, raising

([62]) ECDC: Surveillance report, Hantavirus infection. Annual Epidemiological Report for 2019.

([63]) Jacob et al. Sin Nombre Virus and the Emergence of Other Hantaviruses: A Review of the Biology, Ecology, and Disease of a Zoonotic Pathogen. Biology (Basel). 2023 Nov 9;12(11):1413. doi: 10.3390/biology12111413

([64]) ECDC: Disease information about hantavirus.

the risk of human exposure to infected urine, droppings or saliva. This shift in habitat distribution is heightening the potential for spillover events.

Extreme weather events are becoming more frequent due to climate change and also play a crucial role in hantavirus transmission. Heavy rainfall and floods can displace rodent populations, forcing them into human dwellings where they shed the virus in environments with a greater human presence. Conversely, droughts may lead rodents to seek food and water closer to human settlements (intensifying the risk of exposure) and may also increase airborne transmission, because fresh rodent urine, droppings, nesting materials and saliva are stirred up and inhaled.

Wildfires are also intensified by climate change, can devastate rodent habitats and force them into new ecological niches, thereby altering virus transmission dynamics. Such shifts can alter established transmission dynamics and create new exposure risks for human populations.

The increasing human exposure to hantaviruses is also linked to land-use changes, deforestation and agricultural expansion. All of these bring human populations into closer contact with rodent habitats.

5.5.4. MCM availability

Vaccines

Advances have been made in the study of *Hantaviridae* (including the development of specific vaccines), but no vaccines for these viruses are currently available in the EU. However, regulatory approvals and vaccination programmes have been established in other jurisdictions.

South Korea has licensed the inactivated Hantaan virus vaccine (Hantavax), which has been in use since the 1990s (primarily for military personnel and high-risk groups). It is effective in reducing cases but requires multiple doses and regular boosters due to waning immunity.

China has approved both monovalent and bivalent inactivated vaccines that target the Hantaan and Seoul viruses. These are included in national immunisation programmes in endemic areas and have contributed to a marked decrease in HFRS cases.

There is no approved vaccine in the US but several candidates do exist there. These include DNA-based vaccines and viral-vector platforms that target the Sin Nombre and Andes viruses. They have reached early-phase clinical trials, largely driven by federal research initiatives with dual public health and biodefence goals.

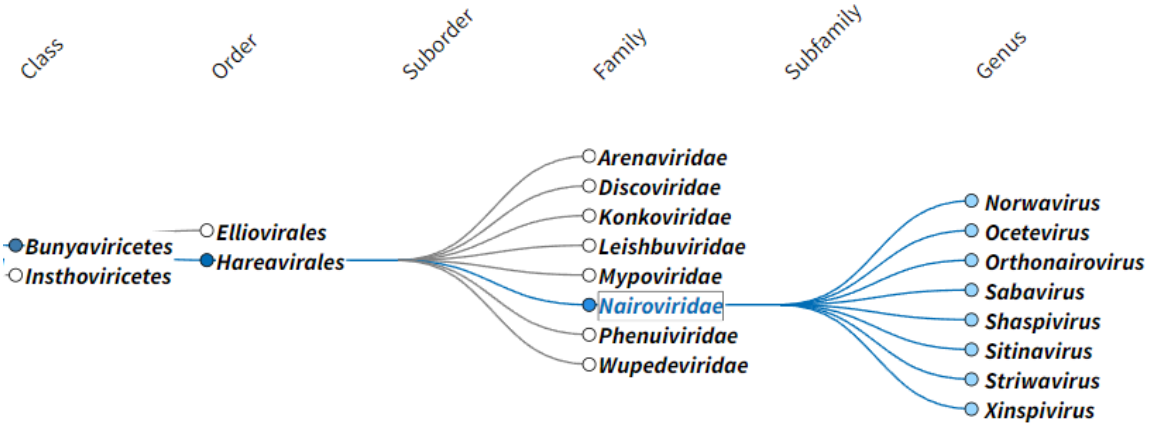
Therapeutics

Advances have been made in the study of *Hantaviridae* (including the development of specific therapeutics), but there are no approved antivirals to treat hantavirus infection**.** Ribavirin has been used off-label in some cases, with mixed clinical outcomes and unclear benefit.

Several therapeutic candidates for *Hantaviridae* are in late-stage development. These include (1) monoclonal antibodies such as a US DoD-sponsored broad-spectrum

anti-hantavirus mAb; and (2) small-molecule antivirals like favipiravir, which has shown efficacy in animal models and is considered for repurposing despite being used off-label in some viral infections. In addition, immunomodulators like tocilizumab and vandetanib, which were originally developed for other indications, are being explored for severe disease management, particularly to address vascular leakage and cytokine dysregulation in HCPS.

5.6. *Nairoviridae*



5.6.1. Main representatives

Nairoviridae comprise various genera and species that are notable pathogens impacting humans and animals. These viruses are primarily transmitted by arthropod vectors, including ticks. The priority pathogen within this family is the Crimean-Congo haemorrhagic fever virus (CCHFV) (genus Orthonairovirus), which can cause severe haemorrhagic fever in humans and poses a significant public health threat in endemic regions, with a case fatality rate of up to 40% ([65]).

5.6.2. Epidemiological situation

CCHFV is widely distributed throughout Africa, the Balkans, the Middle East and western and south-central Asia. In the EU, CCHFV is endemic in the Balkan region and sporadic cases have been reported in Bulgaria, Spain and Portugal.

The *Hyalomma marginatum* (the main vector) and *Hyalomma lusitanicum* ticks are both present in the south-eastern part of the Iberian Peninsula (Spain and Portugal). In 2016, the first cases of CCHFV were detected in Spain. Spain has since reported 19 sporadic and locally acquired cases.

5.6.3. Impact of climate change

Climate change is significantly affecting the dynamics of *Nairoviridae*, particularly the transmission and geographic spread of CCHFV. One of the most critical climate-related factors is the latitudinal and altitudinal expansion of *Hyalomma* tick habitats. Rising ambient temperatures, milder winters and increasing relative humidity are enabling these ticks to survive and establish populations in regions where they were previously unable to persist. *Hyalomma marginatum* was traditionally confined to parts of Africa, Asia and southern Europe but has now been reported in central and even northern Europe. Mild winters and increased humidity create favourable conditions for tick survival. Prolonged warm seasons extend the period during which they can actively seek hosts and transmit the virus.

([65]) https://www.who.int/news-room/fact-sheets/detail/crimean-congo-haemorrhagic-fever.

Climate-driven changes in land use (including desertification and altered agricultural practices) are reshaping habitats in ways that support tick proliferation.

Changes in wildlife and livestock movement patterns are also contributing to the spread of CCHFV. Migratory birds disperse *Hyalomma* ticks across large distances. Climate change alters migration routes and timings and may thus facilitate the introduction of infected ticks into new areas. Livestock (particularly cattle) are important hosts for ticks and may transport them across borders due to shifting grazing practices, increased global travel and trade, or climate-driven agricultural changes.

5.6.4. MCM availability

Vaccines

No licensed vaccines for CCHFV are currently available in the EU. Bulgaria has used a locally produced inactivated CCHF vaccine since 1974. This is administered to high-risk groups but, while it does reduce disease incidence, its use remains limited due to its derivation from mouse brain tissue and lack of international approval.

Several vaccine candidates are under development, including inactivated, DNA-based and viral-vector-based vaccines. A DNA vaccine encoding the CCHFV glycoprotein precursor has demonstrated protective efficacy in preclinical lethal mouse models.

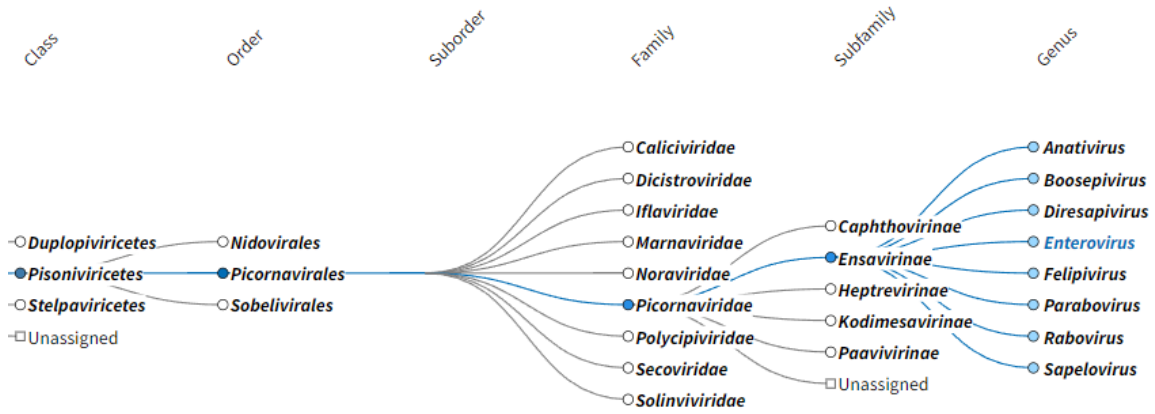
Therapeutics

There are no approved therapeutics for CCHFV.

Clinical guidelines often recommend supportive care as the primary treatment strategy – focusing on managing symptoms, maintaining fluid balance and treating secondary infections. Efforts to develop specific antiviral treatments or improve the effectiveness of existing options are ongoing. Off-label use of ribavirin, an antiviral drug, has been used with some success in reducing mortality in CCHF cases when administered early, but its efficacy remains inconclusive. Clinical use continues to be off-label and case-dependent.

The availability of targeted therapeutics for CCHFV is still limited.

5.7. *Picornaviridae*



5.7.1. *Main representatives*

The *Picornaviridae* family is responsible for a wide range of diseases in humans and animals, including respiratory and gastrointestinal infections. Poliovirus is considered the priority pathogen within this family, while Enteroviruses D68 and A71 are prototype pathogens. This viral family also includes Hepatitis A, which is a disease covered by the EU's epidemiological surveillance system.

HERA's prioritisation of the *Picornaviridae* family reflects both the substantial health burden posed by these viruses within the EU and the emerging threat of non-polio enteroviruses – despite the WHO having classified *Picornaviridae* as having only a medium risk of causing a PHEIC. Picornaviruses (particularly rhinoviruses and enteroviruses) are among the most common viral causes of acute respiratory infections in young children in Europe. Rhinoviruses are frequently identified as the leading cause of such infections in children under five years of age in the EU/EEA. Furthermore, the mode of transmission of enterovirus infections, which can be transmitted from person to person by direct contact, makes outbreaks more difficult to control. Poliovirus, a member of this family, remains the subject of a currently ongoing PHEIC, which was first declared in 2014.

Poliomyelitis has historically been a major cause of morbidity, acute paralysis and lifelong disabilities, but large-scale immunisation programmes have eliminated polio from most areas of the world.

EV-D68 infections have been linked to acute flaccid paralysis / acute flaccid myelitis (AFP/AFM) since a major outbreak in 2014 in North America. This was associated with respiratory and neurological symptoms, particularly in children.

EV-A71 is the most neuropathogenic non-polio enterovirus in humans. It causes a variety of neurological diseases, including aseptic meningitis, encephalitis, brainstem encephalitis and poliomyelitis-like paralysis.

5.7.2. Epidemiological situation

Polio:

The ECDC ([66]) assesses the overall risk among vaccinated populations as very low, both in areas of high vaccination coverage and in areas of low vaccination coverage in the EU/EEA. The overall risk among undervaccinated and unvaccinated populations is assessed as low in areas with high vaccination coverage and moderate in areas with low vaccination coverage. If polio cases were to be detected or clear evidence of sustained community transmission were to emerge, the impact on public health services across the EU/EEA would be significant. Mobilisation of public health resources would be required to control the outbreak. This would include strengthening vaccination campaigns and surveillance programmes; managing polio cases in hospitals and in the community; increasing vaccine stockpiles; revising national poliomyelitis plans; and carrying out continuous assessments until the event is considered to be concluded. Key risk factors for polio in EU/EEA remain the importation of cases and suboptimal immunisation of the population, because that may result in the virus becoming transmissible within communities.

Non-polio enteroviruses:

Comprehensive data on the incidence of non-polio enterovirus infections in EU/EEA countries are currently not available ([67]). It is likely that there is ongoing widespread transmission of different enterovirus species and serotypes (including EV-A71 and EV-D68) in Europe and that most detected and reported cases represent the more severe clinical disease.

In the EU, the circulation of EV-A71 has not been associated with epidemics since the 1970s (when large outbreaks occurred in Bulgaria and Hungary) but rather with sporadic and often mild cases that present mainly with hand, foot and mouth disease (HFMD). In 2016, a notable outbreak with neurological complications caused by an enterovirus was detected in Spain, affecting more than 80 children up to 10 years of age and leading to hospitalisations (sometime in intensive care units). The evidence suggested that the epidemiological pattern of EV-A71 in Europe is changing due to virus molecular evolution and to an increasing likelihood of new virus strains being imported from outside the EU.

Only limited information is available on the earlier and current circulation of EV-D68 in the EU because this infection is not a notifiable disease in many EU/EEA countries (i.e. confirmed cases are not routinely reported to public health authorities). Furthermore, EV-D68 can cause a wide range of symptoms (ranging from mild respiratory illness to severe neurological complications like Acute Flaccid Myelitis) and this makes it difficult to differentiate it from other illnesses, thus further hindering accurate reporting.

EV-D68 is nevertheless known to circulate in Europe. Active case finding efforts (like the EV-D68 task force in Wales) have identified significantly more severe infections than

([66]) https://www.ecdc.europa.eu/sites/default/files/documents/assessing-risk-public-health-detection-poliovirus-wastewater.pdf.
([67]) https://www.ecdc.europa.eu/en/publications-data/rapid-risk-assessment-enterovirus-detections-associated-severe-neurological.

passively reported cases. D68 probably contributes to a significant portion of respiratory illnesses and potentially some severe neurological complications within the EU/EEA.

Regular EV-D68 upsurges have been reported in Europe since 2010, but they largely ceased during the COVID-19 pandemic. EV-D68 circulation in Europe has followed a biennial epidemic pattern confined to the autumn season of even-numbered years, but the autumn of 2019 showed an unexpected upsurge in EV-D68 infections ([68]).

Hospital-based surveillance efforts are underway. The European Non-Polio Enterovirus Network (ENPEN) is implementing hospital-based surveillance in order to gain a better understanding of the disease burden (including potential progression to severe cases like AFM). These ongoing efforts will be instrumental in understanding the true burden of this virus and implementing effective public health measures.

5.7.3. Impact of climate change

Overall, climate change could lead to increased transmission of picornaviruses by enhancing environmental stability, altering disease seasonality and increasing risks from waterborne outbreaks. Warmer temperatures and increased humidity can enhance the stability of many picornaviruses in the environment, prolonging their survival on surfaces and in water. This could lead to more frequent outbreaks (especially in crowded environments like schools and health) and an increase in incidence and geographic range due to climate-driven changes in human mobility and environmental conditions.

Climate-driven changes in human settlements and livestock farming practices may increase exposure to enteric picornaviruses (such as those causing HFMD) in areas where both humans and animals are in close proximity.

5.7.4. MCM availability

Vaccines

The primary vaccine against polio that is authorised and recommended for use in the EU/EEA is the inactivated poliovirus vaccine (IPV), which is widely used in most countries. The oral poliovirus vaccine (OPV) is still used globally, particularly for outbreak responses and in areas where polio remains a concern.

A newer version of OPV (novel oral poliovirus vaccine – nOPV) has been developed to reduce the risk of vaccine-derived poliovirus by decreasing the virus's ability to replicate. This is primarily used for type 2 poliovirus, where the risk of vaccine-derived outbreaks has been more common.

IPV is given by injection, is included in routine immunisation schedules and is often combined with other antigens such as DTP and Hib, thus providing strong immunity with an excellent safety profile.

OPV is administered orally and is effective in inducing intestinal immunity and reducing virus transmission, but it also carries a rare risk of vaccine-derived poliovirus. The EU follows WHO recommendations, emphasising IPV in national schedules while supporting

([68]) https://pubmed.ncbi.nlm.nih.gov/34763750/.

global polio eradication efforts and maintaining high vaccination coverage and disease surveillance.

There is no commercially available vaccine that is specifically designed to prevent EV-D68 or EV-A71 infections.

Therapeutics

There is no specific treatment for people with respiratory illness caused by polio, EV-D68 or EV-A71. Indeed, no antiviral medications are currently available.

6. CONCLUSION OF CHAPTER I

The emergence and spread of new zoonotic viruses remain a persistent and growing concern. It is driven by global trends such as increased human encroachment into wildlife habitats, rapid urbanisation, global travel, biodiversity loss, environmental degradation and climate change. These trends amplify the risk of spillover events, accelerate transmission and complicate containment efforts (as evidenced especially in the early stages of the COVID-19 pandemic).

Significant regulatory, scientific and organisational advances have improved pandemic preparedness and response capacities, but these gains are increasingly offset by structural vulnerabilities: health workforce shortages, fragile supply chains, funding fluctuations and incomplete institutionalisation of lessons learned. Moreover, the COVID-19 pandemic also exposed (and sometimes exacerbated) vulnerabilities and existing inequalities in healthcare access and vaccine distribution. The erosion of post-pandemic momentum risks undermining hard-won gains in public health preparedness, particularly in low-income and middle-income countries.

Within the EU, ecological and climatic shifts are altering the transmission dynamics of several high-impact pathogens, including vector-borne viruses that are now established in parts of Europe. This evolving landscape underscores the need for sustained vigilance and regionally adapted preparedness strategies.

This chapter has identified and prioritised 12 viral families with epidemic and pandemic potential, grouped into two severity tiers. Five of these families (*Coronaviridae, Orthomyxoviridae, Flaviviridae, Filoviridae,* and *Poxviridae*) have been designated as being of highest priority due to their demonstrated or emerging threat potential to the EU.

It is important to note that this document recognises that not all serious infectious disease threats will result in pandemics. Many (especially vector-borne pathogens) may instead cause recurrent regional outbreaks or health emergencies. The dual assessment of both the epidemic and pandemic potential has therefore ensured that both global and EU-relevant threats are captured appropriately.

Going forward, this prioritisation framework provides a strategic foundation for HERA's work on R&D, MCM development, procurement planning and cross-sectoral coordination when targeting the viral families of epidemic and pandemic potential. Sustained investment in preparedness, at both EU and global levels, remains essential in order to ensure timely, equitable and effective responses to future health threats (including ensuring the general availability of and access to MCM).

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CHAPTER II: ARMED CONFLICT-RELATED AND CHEMICAL, BIOLOGICAL, RADIOLOGICAL AND NUCLEAR THREATS

Assessing preparedness for CBRN incidents is a key component of improving EU health security. The importance of preparedness work was most recently underscored by the Niinistö Report. Russia's war of aggression against Ukraine and the generally more volatile geopolitical situation further increase its relevance.

This Comprehensive Assessment provides an overview of current CBRN threats. It also addresses emerging threats as well as the MCM that can be used against these current and emerging threats. It has been developed in close consultation with EU Member States through an iterative process. The more extensive, detailed chapter is not publicly available because it contains classified information and is of a sensitive nature.

The analysis provides information on commercialised MCM and the development pipeline, thus enabling both the Commission and the EU Member States to identify gaps in the availability and coverage of MCM. This permits the Commission to better channel funding from Horizon Europe, EU4Health and future programmes to the most underfunded areas in CBRN research and development in order to maximize impact and added value.

The document covers several categories of threats.

- **Biological agents** (including anthrax, smallpox, haemorrhagic fevers and plague) are known for their high case fatality rates, potential for weaponisation and social disruption. They remain a primary focus for biodefence initiatives.
- **Chemical warfare agents** (including nerve agents, blister agents, pharmaceutical-based agents and vesicants) have been used during the civil war in Syria and targeted attacks in Europe and Asia over the past decade.
- **Biotoxins** are covered by both the Chemical and the Biological Weapons Conventions. They are at the intersection of biological and chemical agents. Several incidents in Europe since 2018 (including in Germany, Norway, the UK and other countries), have underscored the need for more MCM in order to protect people from and treat biotoxin exposure and injury.
- **Emerging biological and chemical threats**. Rapid progress in biotechnology and computational chemistry is opening up promising advances in the development of medicines but also bringing potential threats.
- **Radiological and nuclear threats** are an increasing concern in Ukraine and the EU. The situation around the Zaporizhzhya nuclear power plant is of particular concern.

With rescEU, the Commission has made substantial progress in stockpiling the personal protective equipment, detection and decontamination tools, vaccines and therapeutics needed in the event of CBRN incidents. The chapter on CBRN is a first approach to quantifying possible needs for MCM or selected threats in the event of an incident with each agent. For this purpose, it describes MCM that are currently under development and already on the market. This is underpinned by regular CBRN workshops on MCM with EU Member States that include discussions on the relevant parts of this chapter. The inputs from these technical discussions are then used to improve the chapter, which will also be regularly updated.

By preparing for both established and emerging threats (including intentional threats) the Commission can help EU Member States to enhance readiness and resilience. This proactive approach enables the EU to stay ahead of potential threats and protect the health and security of its populations.

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CHAPTER III: ANTIMICROBIAL RESISTANCE

1. INTRODUCTION

Antimicrobial resistance (AMR) poses a significant threat to public health. The emergence and spread of resistant pathogens can render many existing antimicrobial agents ineffective, leading to increased morbidity, mortality and healthcare costs.

Addressing AMR requires a holistic and interdisciplinary strategy. This is emphasised by the One Health approach, which recognises the interconnectedness of human, animal and environmental health in the spread of resistant pathogens. The Commission's Communication of 29 June 2017 'A European One Health Action Plan against AMR' outlines over 70 measures covering human health, animal health and the environment. Progress in carrying out these measures has been regularly monitored. Furthermore, the 2023 Council Recommendation on stepping up EU actions to combat AMR in a One Health approach ([69]) includes a series of additional measures to be implemented by the Commission and EU Member States. The Commission and EU Member States are particularly encouraged to (1) reinforce the surveillance and monitoring of AMR and antimicrobial consumption; (2) strengthen infection prevention and control as well as antimicrobial stewardship and prudent use of antimicrobials; (3) recommend targets for antimicrobial consumption and AMR in human health; and (4) improve awareness, education and training. They are also encouraged to foster research and development, and to offer incentives for innovation and access to antimicrobials and other AMR MCM.

The prioritisation proposed in the present chapter aims to contribute to the comprehensive strategy of the Commission and EU Member States against AMR by identifying priority pathogens that HERA should consider in its decision-making on interventions to improve innovation and/or access to MCM.

The present chapter summarises the pre-existing prioritisation efforts, on which it builds, as well as the available analyses of the current MCM landscape and pipeline. It then describes for each priority pathogen the epidemiological situation in the EU/EEA, including significant trends, unusual cases and outbreaks of AMR-related infections up to 5 October 2025.

This chapter focuses on infections with resistant bacterial and fungal microorganisms. It does not address antiparasitic resistance because of the lower health burden in the EU/EEA. It also does not address antiviral drug resistance, because priority viral pathogens are addressed in the first chapter of this prioritisation report.

Furthermore, this chapter does not describe the measures and interventions implemented by the Commission and other stakeholders to address the lack of access to and innovation in AMR MCM. Nor does it address other types of interventions like non-MCM infection prevention and control measures, antibiotic stewardship or measures to raise awareness among the public and professionals.

([69]) Council recommendation on stepping up EU actions to combat AMR in a One Health approach - June 2023.

2. AMR BURDEN AND GLOBAL CONTEXT

2.1. AMR health burden

In September 2024, the Lancet published an analysis of the global burden of AMR from 1990 to 2021, along with forecasts to 2050 ([70]). In 2021, bacterial AMR was globally linked to an estimated 4.71 million deaths, including 1.14 million that were directly attributed to AMR infections. The highest burden of AMR bacterial infections was represented by bloodstream and respiratory tract infections.

The burden of AMR remains particularly severe in low-income and middle-income countries (LMICs), where the healthcare systems are often under resourced. However, high-income countries also face significant challenges with documented increasing rates of AMR. In the EU/EEA, more than 35 000 people die from AMR infections each year and this number is increasing, according to the ECDC ([71]). Between 2016 and 2020, the health burden of AMR was about 1 000 000 DALY (disability-adjusted life years) ([72]), with the highest age-group-specific burden in infants and older people. The health burden of infections with antibiotic-resistant bacteria in the EU is comparable with that of influenza, tuberculosis and HIV/AIDS combined, with 70% of cases of infections with antibiotic-resistant bacteria being healthcare-associated infections. The overall burden of infections with antibiotic-resistant bacteria was estimated to be highest in Greece, Italy and Romania, and impacts empiric therapy for common infections in these EU Member States.

Looking ahead, the forecasts until 2050 suggest that AMR could become one of the leading causes of death globally, potentially resulting in 10 million deaths annually. This underscores the urgent need for comprehensive global action to tackle the rise of AMR through improved infection prevention and control, better antimicrobial stewardship and increased funding particularly through innovative new models, such as both push initiatives (which support throughout the research and development process) and pull initiatives (which offer financial incentives to bring new MCM to market). All these efforts are essential to drive the development of new antibiotics, diagnostics and vaccines needed to combat AMR effectively.

2.2. Global context and impact on AMR

2.2.1. COVID-19 pandemic

During the COVID-19 pandemic, the EU/EEA observed significant shifts in AMR and antibiotic consumption patterns ([73]).

In the community, the consumption of antibacterials decreased in almost all but one EU/EEA country. Non-pharmaceutical interventions (e.g. physical distancing) were associated with reductions in community-acquired infections, reduced need for antibiotics

([70]) Global burden of bacterial antimicrobial resistance 1990–2021: a systematic analysis with forecasts to 2050 - The Lancet.

([71]) Assessing the health burden of infections with antibiotic-resistant bacteria in the EU/EEA, 2016-2020 (europa.eu).

([72]) The disability-adjusted life year or DALY is a summary measure of population health. DALYs are the sum of the years of life lost due to premature mortality and years of life lived with disability.

([73]) Decrease in community antibiotic consumption during the COVID-19 pandemic, EU/EEA, 2020 - PMC (nih.gov).

and reduced access to medical services. Reductions in diagnostic and treatment services, and limited access to antibacterials, could all have decreased consumption. However, this decrease appears to have been only temporary and the EU/EEA-level of consumption was already back at pre-pandemic levels in 2022 ([74]). The resurgence of both viral and bacterial respiratory tract infections following the pandemic (potentially linked to the lifting of non-pharmaceutical interventions, including the use of face masks) might partly explain this rebound in antibiotic consumption.

In hospitals, changes were less consistent across countries. In particular, there was an increased use of last-resort antibiotics (such as carbapenems) and a rise in infections with multidrug-resistant (MDR) bacteria and fungi. The increasing use of last-line antibiotics could have been due to several factors, including an increased proportion of patients with severe disease as well as constraints on hospital infection prevention and control (IPC) practices (high hospital patient load and staff absenteeism due to COVID-19 could have limited the time and attention accorded to IPC). In addition, new procedures for using personal protective equipment (PPE) during the COVID-19 pandemic (due to constraints on PPE supplies) could have facilitated the spread of infections with MDR pathogens in healthcare settings. Data from the European Antimicrobial Resistance Surveillance Network (EARS-Net) revealed a 57% rise in bloodstream infections caused by *Acinetobacter* species in the EU/EEA during the first two years of the COVID-19 pandemic (2020–2021) compared with the preceding two years. This increase was largely driven by carbapenem-resistant *Acinetobacter* spp.. ([75]).

2.2.2. Conflicts and forced displacements

Human conflict is an important driver of AMR and has consequences for healthcare systems globally ([76]) ([77]). The threat of AMR is a pressing issue in Ukraine, where healthcare-associated infections caused by MDR organisms are a major concern ([78]). Infections in war casualties and AMR risk have impacts on global public health. The ongoing war has contributed to the emergence of a reservoir of infections with MDR gram-negative bacteria in Ukraine and Russia, and there is a risk of regional and international spread ([79]).

In 2022, EU/EEA countries reported the detection of MDR organisms in patients recently hospitalised in Ukraine. However, the impact of the war in Ukraine on the data reported to EARS-Net remains unclear.

Many studies have reported cases of infections with MDR pathogens in patients transferred from hospitals in Ukraine to several EU Member States. For example, in Denmark, genotypic characterisation showed that 21% of the total carbapenemase-producing

([74]) Eurosurveillance | Rebound in community antibiotic consumption after the observed decrease during the COVID-19 pandemic, EU/EEA, 2022.
([75]) Large increase in bloodstream infections with carbapenem-resistant Acinetobacter species during the first 2 years of the COVID-19 pandemic, EU/EEA, 2020 and 2021 (eurosurveillange.org)
([76]) The contribution of human conflict to the development of antimicrobial resistance | Communications Medicine (nature.com).
([77]) The impact of armed conflict on the development and global spread of antibiotic resistance: a systematic review - PubMed
([78]) War impact on antimicrobial resistance and bacteriological profile of wound infections in Ukraine | Communications Medicine
([79]) Ukraine war and antimicrobial resistance - ScienceDirect.

organisms identified in Denmark were from patients originating in Ukraine ([80]). On 8 March 2022, the ECDC published a report that recommended that hospitalised patients in the EU/EEA that have been transferred there from hospitals in Ukraine should be pre-emptively isolated and screened for MDR organisms ([81]).

In addition to the impact of the war in Ukraine, other forced migrations due to conflict and wars have also an impact on the global increase of AMR ([82]). For example, forcibly displaced persons may be at increased risk of both tuberculosis (TB) and MDR-TB due to the breakdown of local healthcare systems and their exposure to TB and MDRTB during their migration trajectory due to overcrowding, incarceration, or detention ([83]). The current conflict in the Gaza Strip poses multiple challenges related to AMR ([84]). The Gaza Strip faces a constant influx of injured individuals with heavily contaminated wounds; limited resources for managing the deceased; overcrowded and/or destroyed hospitals; critical shortages of basic medical equipment and essential antibiotics; and a lack of transmission-based precautions. These factors exacerbate the transmission of infections – both in healthcare facilities and in the community ([85]). Finally, heavy metals from munitions, military vehicles and weapons can select for bacterial strains with co-resistance to both antibiotics and metals ([86]).

Public health surveillance gaps as well as cultural and language barriers are hindering effective communication and treatment adherence, thus increasing the risk of AMR emerging. Coordinated international efforts are needed in order to improve healthcare infrastructure, enhance surveillance and promote the rational use of antibiotics among displaced populations.

2.2.3. Climate change

Climate change is increasingly recognised as a significant driver of AMR. Rising global temperatures and extreme weather events can alter ecosystems, facilitating the spread of infectious diseases (including those caused by drug-resistant pathogens) ([87]). Extreme weather events, such as floods, heighten human exposure to bacteria with antibiotic-resistant genes found in contaminated soil and wastewater. These conditions not only facilitate the spread of antimicrobial-resistant pathogens but can also expose bacteria to heavy metals, which can drive further development of resistance. In particular, metal-resistant genes are often linked to antibiotic-resistant genes within mobile genetic elements (e.g. gene cassettes), thus enabling bacteria to develop and transfer resistance more rapidly.

Climate change exacerbates malnutrition, weakening immune systems and making individuals more vulnerable to infections. This leads to more frequent and severe diseases,

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([80]) Genotypic characterisation of carbapenemase-producing organisms obtained in Denmark from patients associated with the war in Ukraine - ScienceDirect.

([81]) ECDC technical report Operational public health considerations for the prevention and control of infectious diseases in the context of Russia's aggression towards Ukraine, 8 March 2022.

([82]) Antimicrobial Resistance and Human Mobility - PMC

([83]) Antimicrobial Resistance and Human Mobility – PMC (nih.gov).

([84]) WHO EMRO - Tackling antimicrobial resistance and the collapse of microbiology diagnostics in Gaza

([85]) Antimicrobial resistance in the ongoing Gaza war: a silent threat – PubMed.

([86]) Heavy Metal Toxicity in Armed Conflicts Potentiates AMR in A. baumannii by Selecting for Antibiotic and Heavy Metal Co-resistance Mechanisms - PMC

([87]) Antibiotic resistance is a growing threat – is climate change making it worse?

increasing the demand for antibiotics and other antimicrobials. Furthermore, rising food insecurity can lead to increased antibiotic use in food production to prevent disease in crop farming and livestock.

The thawing of permafrost raises concerns about the potential spread of AMR through the exchange of genetic material between microorganisms in the permafrost containing pre-existing AMR genes and contemporary bacteria ([88]).

3. PRIORITY-SETTING INITIATIVES

HERA's prioritisation of AMR threats builds extensively on other European and global priority-setting initiatives, and on the findings from the epidemiological surveillance carried out by the ECDC in the EU.

Since 2022, HERA has partnered with the WHO headquarters to provide support to the development of activities aiming at informing and guiding the R&D of new AMR MCM. These activities include the WHO's fungal priority pathogens list (FPPL) ([89]) and the WHO's bacterial priority pathogens list (BPPL) ([90]) and the WHO's fungal priority pathogens list (FPPL) ([91]) to guide research, development and public health actions (published in 2022 and 2024 respectively).

Both the BPPL and FPPL were created with the purpose of signalling to researchers, pharmaceutical companies and funding agencies which pathogens pose the greatest risk and where R&D investments are urgently needed in order to develop new antibiotics. Since its first publication in 2017, the BPPL has had a substantial impact on global awareness and has been used to inform policy and funding decisions aimed at addressing the critical gaps in the treatment of infections with antibiotic-resistant bacteria.

The WHO has created the BPPL using a scientific decision-making method called Multicriteria Decision Analysis (MCDA) and input from global experts to carefully evaluate and rank bacterial threats based on a range of attributes (including mortality, non-fatal health burden, transmissibility, incidence, trends of resistance, preventability in the community, diagnosis, treatability and pipeline). This process has ensured that the list is based on the best available evidence and that each pathogen is evaluated fairly and transparently.

This careful and systematic approach ensures that the WHO's pathogens priority lists are a trustworthy and up-to-date resource and are therefore endorsed by HERA to inform its decision-making on interventions to support the R&D&I of AMR MCM.

([88]) Emergent biogeochemical risks from Arctic permafrost degradation | Nature Climate Change.
([89]) WHO fungal priority pathogens list to guide research, development and public health action.
([90]) WHO Bacterial Priority: Bacterial pathogens of public health importance to guide research, development and strategies to prevent and control AMR.
([91]) WHO fungal priority pathogens list to guide research, development and public health action.

The present assessment does not cover the various initiatives to prioritise pathogens with AMR and countermeasures in animal health (e.g. the prioritisation of diseases for which vaccines could reduce antimicrobial use in cattle, sheep and goats ([92])).

This chapter focuses on prioritisation at EU and global level. However, some EU Member States describe their priorities (in terms of pathogens, antibiotics and other MCM) in their national action plans against AMR. The Commission published an overview report of these national actions plans in November 2022 ([93]).

3.1. WHO bacterial priority pathogens list

Building on the 2017 edition, the WHO published a new version of the BPPL in 2024 (**Error! Bookmark not defined.**). The new list updates and enhances the prioritisation of antibiotic-resistant bacterial pathogens to address the evolving challenges of antibiotic resistance. The list classifies bacteria into three categories according to the urgency of need for new antimicrobials and public health strategies: critical, high-priority and medium-priority. In total, the list covers 24 pathogens, spanning 15 families of AMR bacterial pathogens (**Error! Reference source not found.**).

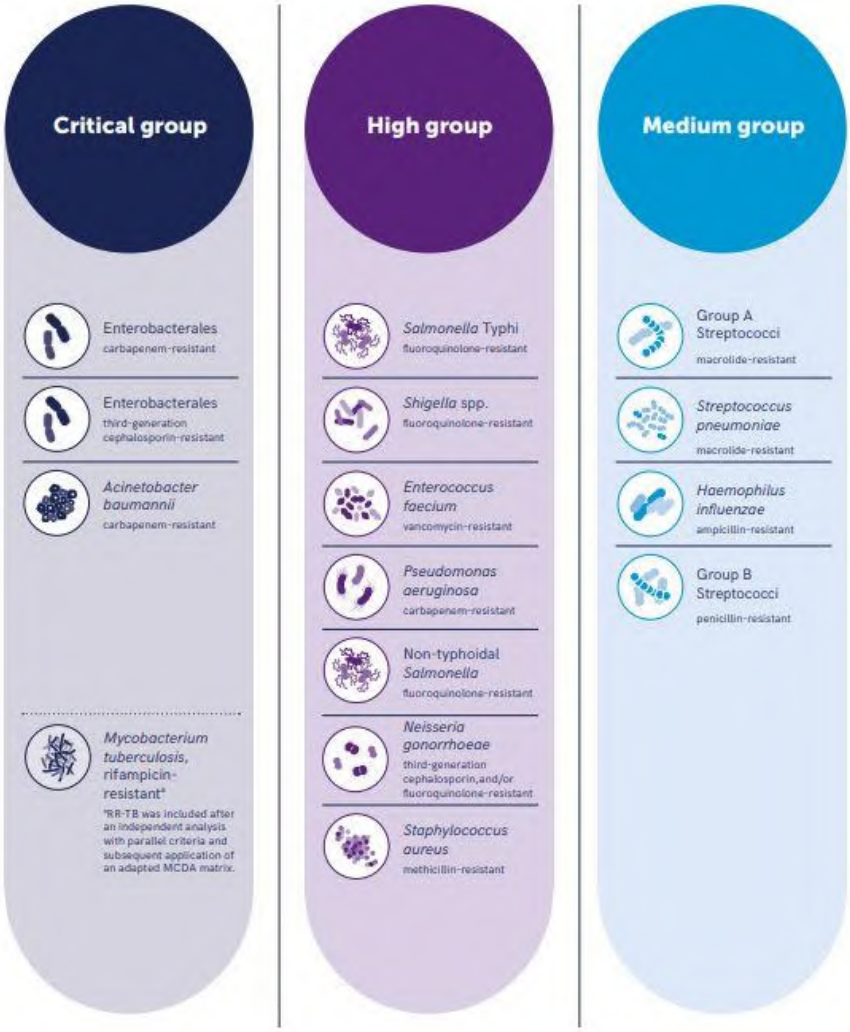
The critical group includes MDR bacteria and bacteria that are resistant to last-resort antibiotics, which can transfer resistance genes and pose a particular global burden. Besides rifampicin-resistant tuberculosis (RR-TB), most bacteria present in the critical group are associated with hospital-acquired infections.

The high-priority categories include other increasingly drug-resistant bacteria, some of which cause more common, community-acquired diseases such as sexually transmitted infections (*Shigella* spp, *N. gonorrhoea*) or diarrhoeal diseases (non-typhoidal *Salmonella).*

Figure 4. WHO bacterial priority pathogens list, 2024. Source: WHO (**Error! Bookmark not defined.**).

([92]) Report of the meeting of the OIE ad hoc group on prioritisation of diseases for which vaccines could reduce antimicrobial use in cattle, sheep and goats, Paris 7-9 May 2018.

([93]) Overview report – Member States' One Health National Action Plans against Antimicrobial Resistance – European Commission.



The BBPL was established according to various criteria, including 'treatability' (the number and quality of antibiotic options available for treatment of an infection by the targeted resistant pathogen) and the 'pipeline' (the extent to which the antibacterial pipeline will in the next 5–7 years address the clinical requirements for treatment of each targeted resistant pathogen). The classification of bacterial pathogens according to these two criteria is indicated below because it is particularly relevant for HERA prioritisation.

Figure 5: Extracted from the 2024 WHO bacterial priority pathogens list.

Table A2.11. Pathogens rated according to level of treatability

High	High–medium	Medium	Medium–low	Low
MR *S. aureus*	FQR *Shigella* spp.	3GCR *E. coli*	CR *K. pneumoniae*	CR *A. baumannii*
Macro-R Group A Streptococci	FQR nontyphoidal *Salmonella*	3GCR *K. pneumoniae*	Carbapenem-R *E. coli*	RR-TB
Macro-R *S. pneumoniae*	Ampi-R *H. influenzae*	VR *E. faecium*	FQR *Salmonella* Typhi	
	Pen-R Group B Streptococci	FQR *N. gonorrhoeae*	CR *P. aeruginosa*	
		3GCR *Enterobacter* spp.	CR *Enterobacter* spp.	
		3GCR *Citrobacter* spp.	3GCR *N. gonorrhoeae*	
		3GCR *Proteus* spp.		
		3GCR *Serratia* spp.		
		3GCR *Morganella* spp.		

FQR, fluoroquinolone-resistant; 3GCR, third-generation cephalosporin-resistant Enterobacterales; CR, carbapenem-resistant; Pen-R, penicillin-resistant; VR, vancomycin-resistant; Macro-R, macrolide resistant ; Ampi-R, ampicillin-resistant; RR-TB rifampicin-resistant tuberculosis

Figure 6: Extracted from the 2024 WHO bacterial priority pathogens list.

Table A2.12. Resistant pathogens rated according to likelihood of potential future treatment availability

Likely	Possible	Unlikely
3GCR *Enterobacter* spp.	3GCR *E. coli*	CR *K. pneumoniae*
3GCR *Proteus* spp.	CR *E. coli*	CR *A. baumannii*
3GCR *Serratia* spp.	3GCR *K. pneumoniae*	FQR *Salmonella* Typhi
Macro-R *S. pneumoniae*	FQR nontyphoidal *Salmonella*	FQR *Shigella* spp.
3GCR *Morganella* spp.	CR *Enterobacter* spp.	VR *E. faecium*
	3GCR *Citrobacter* spp.	CR *P. aeruginosa*
	Macro-R Group A Streptococci	FQR *N. gonorrhoeae*
	Pen-R Group B Streptococci	MR *S. aureus*
		3GCR *N. gonorrhoeae*
		Ampi-R *H. influenzae*
		RR-TB

FQR, fluoroquinolone-resistant; 3GCR, third-generation cephalosporin-resistant Enterobacterales; CR, carbapenem-resistant; Pen-R, penicillin-resistant; VR, vancomycin-resistant; Macro-R, macrolide; Ampi-R, ampicillin-resistant; RR-TB rifampicin-resistant tuberculosis

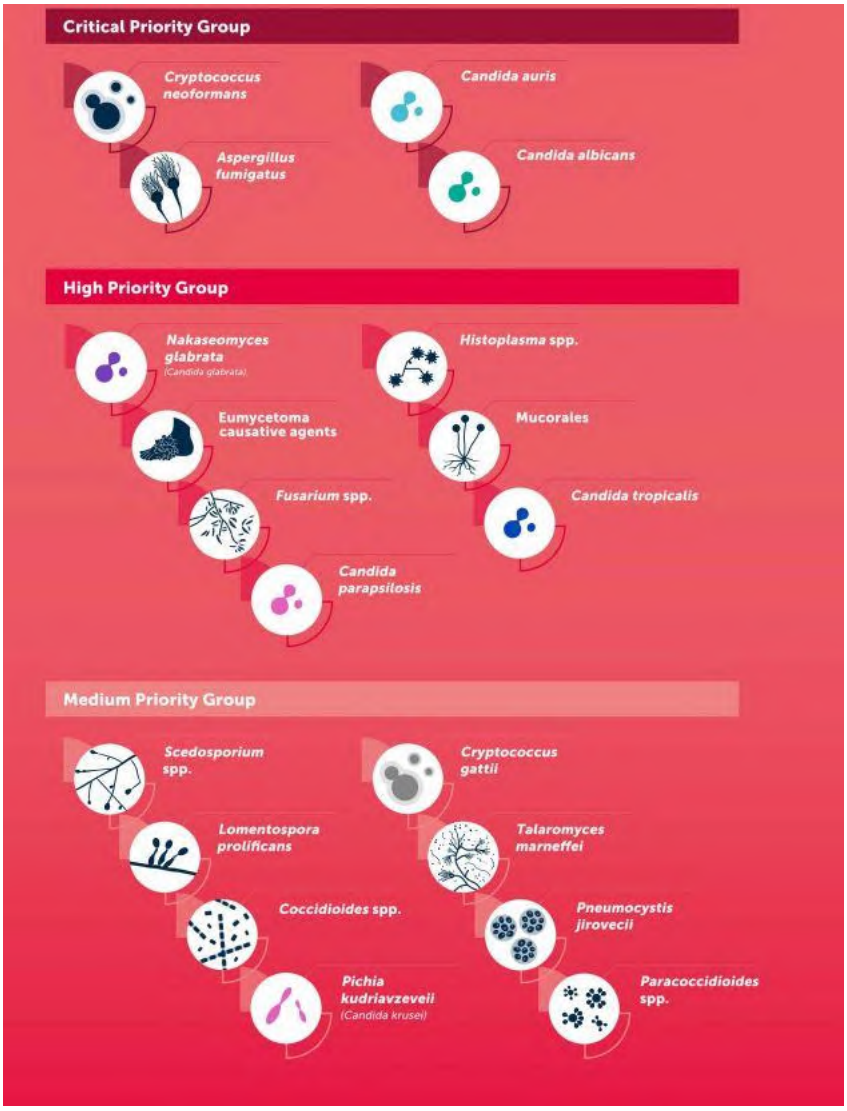
3.2. WHO fungal priority pathogens list

The WHO published its FPPL in 2022 (**Error! Bookmark not defined.**). This was the first-ever global effort to prioritise fungal pathogens in response to the growing challenges of antifungal resistance (**Error! Reference source not found.**). The FPPL categorises fungi (according to the urgency of need for new antifungals and public health strategies) into three priority groups: critical, high and medium. In total, the list covers 19 pathogens, spanning several families of antifungal-resistant fungi. The critical group includes fungi

that are resistant to last-resort antifungal agents, capable of transferring resistance genes and causing a significant global burden. These include *Candida albicans, Candida auris* (currently known as *Candidozyma auris*), *Aspergillus fumigatus* and *Cryptococcus neoformans*.

The high-priority and medium-priority categories include other increasingly drug-resistant fungi that are responsible for common infections, such as *Nakaseomyces glabrata* (*Candida glabrata*), *Cryptococcus gattii* and *Pneumocystis jirovecii*.

Figure 7: WHO fungal priority pathogens list, 2022. Source: WHO (**Error! Bookmark not defined.**).



3.3. AMR pathogens under EU epidemiological surveillance

The list of AMR pathogens prioritised for EU epidemiological surveillance was established by Commission Implementing Decision (EU) 2018/945 of 22 June 2018 ([94]).

([94]) Commission Implementing Decision (EU) 2018/945 of 22 June 2018 on the communicable diseases and related special health issues to be covered by epidemiological surveillance as well as relevant case definitions.

This Commission implementing Decision notably provides that the results of antimicrobial susceptibility tests must be reported as specified in the EU protocol for harmonised monitoring of AMR for:

- human *Salmonella* and *Campylobacter* isolates;
- gonococcal infections;
- shigellosis;
- tuberculosis;
- bloodstream infections due to specific pathogens.

Different surveillance networks, mostly operated by ECDC, are collecting data on AMR, depending on the pathogen-drug combination considered, the affected system, (e.g. bloodstream infections) and the context of transmission (e.g. healthcare-associated infections).

The EARS-Net collects antimicrobial susceptibility data for invasive isolates (blood or cerebrospinal fluid) from selected microorganisms and antimicrobial agent combinations. The surveillance results are published annually in the EARS-Net report ([95]). Data are collected according to a reporting protocol developed by the ECDC in collaboration with EARS-Net participating institutions and in alignment with EU public health policy. The reporting protocol states the microorganism and antimicrobial agent combinations under surveillance. These include the following bacteria:

- *Streptococcus pneumoniae*
- *Staphylococcus aureus*
- *Enterococcus faecalis*
- *Enterococcus faecium*
- *Escherichia coli*
- *Klebsiella pneumoniae*
- *Pseudomonas aeruginosa*
- *Acinetobacter* spp.

EARS-Net collects extensive data on a broader range of bacterial infections and antibiotic combinations relevant to the EU. This approach provides valuable insights into resistance trends in the EU by determining the proportion of resistant isolates within various bacterial species. Not all the microorganism and antimicrobial agent combinations under surveillance are included in the WHO BPPL, which focuses on specific bacteria–antibiotic combinations of global concern due to the rise of AMR. In particular, *Enterococcus faecalis* is included in EARS-Net's reporting protocol but not in the WHO BPPL; this discrepancy will be addressed in future iterations of this report. Additional surveillance networks include:

- -the European Antimicrobial Resistance Genes Surveillance Network (EURGenNet), which conducts genomic-based surveillance of multidrug-resistant bacteria of public health importance through laboratory surveys of key pathogens (e.g. carbapenem-resistant Enterobacterales and *A. baumannii*);
- the Healthcare-Associated Infections Surveillance Network (HAI-Net), which performs surveillance of healthcare-associated infections (HAIs), including the

([95]) Antimicrobial resistance (AMR) reporting protocol 2024.

surveillance of surgical site infections, intensive care unit HAI and *Clostridioides difficile* infections;

- the European Tuberculosis Surveillance Network, which monitors tuberculosis (including MDR-TB and extensively drug-resistant tuberculosis (XDR-TB));
- the European Gonococcal Antimicrobial Surveillance Programme (Euro-GASP), which focuses on monitoring and reporting on AMR in *Neisseria gonorrhoeae*.

Furthermore, the ECDC collaborates with EFSA for the EU summary report on AMR in zoonotic and indicator bacteria from humans, animals and food ([96]). This report notably collects data on *Salmonella* spp. and Campylobacter isolates from humans and animals.

3.4. Pathogens targeted for incidence reduction in the EU

The 2023 Council Recommendation set targets for the reduction of the incidence of bloodstream infections with three types of antibiotic-resistant bacteria. These concrete and measurable targets are to be achieved by 2030 within the EU [(69)]. The targets for the reduction of incidence of bloodstream infections were set by comparison with 2019 for three antibiotic-resistant bacteria:

- methicillin-resistant S. aureus (MRSA) (target reduction: 15%);
- third-generation cephalosporin-resistant *E. coli* (target reduction: 10%);
- carbapenem-resistant *K. pneumoniae* (target reduction: 5%).

3.5. Priorities regarding antibiotic consumption

The WHO's Access, Watch, Reserve (AWaRe) classification of antibiotics ([97]) was developed in 2017 by the WHO Expert Committee on Selection and Use of Essential Medicines as a tool to support antibiotic stewardship efforts at the local, national and global levels. Antibiotics are classified into three groups (Access, Watch and Reserve) considering the impact of different antibiotics and antibiotic classes on AMR in order to emphasise the importance of their appropriate use. The AWaRe classification is updated every two years. It is intended as a tool for monitoring antibiotic consumption, defining targets and monitoring the effects of stewardship policies that aim to optimise antibiotic use and curb antimicrobial resistance.

The 2023 Council Recommendation also sets targets for a reduction of 20% in total antibiotic consumption (EU population-weighted mean, antibiotics for systemic use) by 2030, and calls on Member States to take appropriate national measures to ensure that at least 65% of each Member State's total annual antibiotic consumption from the 'Access' group of antibiotics, as defined by WHO's AWaRe classification.

([96]) The European Union summary report on antimicrobial resistance in zoonotic and indicator bacteria from humans, animals and food in 2022–2023. 5 March 2025.

([97]) AWaRe classification of antibiotics for evaluation and monitoring of use, 2023 (who.int).

The European Surveillance of Antimicrobial Consumption Network (ESACNet) monitors antibiotic consumption data and publishes the results on an annual basis ([98]), monitoring the progress made towards prudent use of antimicrobials. In addition, the ECDC, EFSA and EMA analyse the potential relationship between the consumption of antimicrobials by humans and animals and the occurrence of AMR (the 'JIACRA' reports) ([99]).

4. MCM PIPELINE AND LANDSCAPE

The AMR MCM pipeline and landscape is well described, notably by the WHO, which has in the last year published several strategic documents, including:

- a WHO review of antibacterial agents in clinical and preclinical development ([100]) published in 2024 and a WHO review of bacterial vaccines ([101]) published in 2022;
- WHO first-ever reports on commercially available and pipeline *in vitro* diagnostics for fungal infections and analysis of antifungal agents in clinical and preclinical development published in April 2025 ([102]) (similar analysis on bacterial diagnostics is under development);
- WHO paediatric drug optimisation (PADO) exercises, which aim to identify key priority products and their preferred product characteristics for R&D ([103]);
- a WHO high-level summary ([104]) of the status of the pipelines for new tuberculosis diagnostics, medicines and vaccines in active development, as of September 2023.

These analyses identify specific and cross-cutting gaps and priorities for R&D and were supported by HERA funding.

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4.1. Antibacterial agents

In June 2024, the WHO published its 2023 'Antibacterial agents in clinical and preclinical development: an overview and analysis' ([105]). The report highlights the fact that the number of antibacterial agents in clinical development increased from 80 in 2021 to 97 in 2023. However, there is still an urgent need for innovative antimicrobial agents to address infections caused by antibiotic-resistant bacteria. These new agents would complement existing antibacterials, helping to ensure that effective treatment options remain available as AMR continues to emerge. The report identified 32 antibacterials in development (56% of the total) against WHO's priority pathogens and 19 (33% of the total) against drug-resistant tuberculosis. Of these 32 antibacterials, only 12 are considered innovative. Of these 12 innovative antibiotics, only 4 (OMN6, cefepime + taniborbactam, ceftibuten +

([98]) Antimicrobial consumption in the EU/EEA (ESAC-Net) - Annual Epidemiological Report for 2022 (europa.eu).
([99]) Simplified summary: JIACRA IV, 2019-2021 (europa.eu).
([100]) 2023 Antibacterial agents in clinical and preclinical development: an overview and analysis (who.int).
([101]) Bacterial vaccines in clinical and preclinical development 2021 (who.int).
([102]) WHO issues its first-ever reports on tests and treatments for fungal infections.
([103]) WHO releases priorities for research and development of age-appropriate antibiotics.
([104]) TB research and innovation (who.int).
([105]) 2023 Antibacterial agents in clinical and preclinical development: an overview and analysis (who.int).

ledaborbactam and xeruborbactam) are active against at least one critical pathogen on WHO's BPPL.

--The current antibacterial pipeline continues to be dominated by β-lactam or βlactam/βlactamase-inhibitor (β-lactam/BLI) combinations (accounting for 47% of traditional antibiotics) with a major gap in activity against metallo-β-lactamase (MBL) producers. The report also highlights an imbalance in the availability of antibacterial agents with paediatric indications and/or formulations against the WHO BPPs when compared with those for adults. A recent WHO-PADO report on antibiotics has also highlighted this.

The study commissioned by HERA and published in January 2023 ([106]) included a comparison of the substances being developed and those on the market, according to their possible activity against target pathogens. This highlights the current gaps in antibiotics (see Figure 5 below).

		Active against key resistant strain						Possibly active against key resistant strain					
	Pathogen	TRL 5	TRL 6	TRL 7	TRL 8	Total in pipeline	Total on market	TRL 5	TRL 6	TRL 7	TRL 8	Total in pipeline	Total on market
Bacteria	*Acinetobacter baumanni* *Carbapenem-resistant*	11	16	5	3	35	2	6	7	3	1	17	3
	Pseudomonas aeruginosa *Carbapenem-resistant*	21	13	12	3	49	2	10	5	5	0	20	5
	Enterobacterales *Carbapenem-resistant* *3rd gen. Cephalosporin-resistant*	18	18	4	5	45	8	7	6	2	1	16	5
	Clostridioides difficile	7	4	11	3	25	5	NA	NA	NA	NA	NA	NA
	Mycobacteria *Multidrug-resistant* *Extensively drug-resistant*	4	3	11	0	18	6	1	1	0	1	3	1
	Enterococcus faecium *Vancomycin-resistant*	8	3	5	1	17	11	2	4	2	0	8	0
	Campylobacter spp *Fluoroquinolone-resistant*	0	0	1	0	1	0	0	0	0	0	0	1
	Helicobacter pylori *Clarithromycin-resistant*	1	3	1	1	6	11	0	0	1	0	1	0
	Neisseria gonorrhoea *Fluoroquinolone-resistant* *3rd gen. Cephalosporin-resistant*	0	2	2	2	6	8	0	0	0	0	0	0
	Salmonella *Fluoroquinolone-resistant*	0	0	0	0	0	3	1	0	0	0	1	0
	Staphylococcus aureus *Methicillin-resistant* *Vancomycin-resistant*	24	7	31	9	71	38	5	4	4	1	14	0
	Shigella spp *Fluoroquinolone-resistant*	0	0	0	0	0	2	0	0	0	0	0	0
	Streptococcus pneumoniae *Penicillin-non-susceptible*	2	2	3	0	7	16	0	0	0	0	0	1
	Haemophilus influenzae *Ampicillin-resistant*	0	0	1	0	1	1	0	0	0	0	0	0
	Gram-negative infections	19	4	1	3	27	6	8	3	0	1	12	3
	Gram-positive infections	6	1	5	0	12	11	2	0	0	0	2	1
Fungi	*Candida auris* *Multidrug-resistant*	1	0	0	1	2	0	0	0	0	0	0	0
	Candida spp *Azole-resistant*	4	1	6	2	13	5	0	0	0	0	0	0
	Aspergillus fumigatus *Azole-resistant*	5	0	5	1	11	3	0	0	0	0	0	0
	Cyptococcus spp *Azole-resistant*	1	1	2	0	4	1	0	0	0	0	0	0
	Pneumocystis jirovecii *Multidrug-resistant*	0	0	0	0	0	0	0	0	0	0	0	0
	Mucormycetes *Azole-resistant* *Echinocandin-resistant*	1	0	0	0	1	0	0	0	0	0	0	0
	Histoplasma spp *Azole-resistant*	0	0	0	0	0	1	0	0	0	0	0	0
Parasite	*Toxoplasma gondii* *Drug-resistant*	0	0	0	0	0	1	0	0	0	0	0	0
Virus	*Human Immunodefficiency Virus* *Drug-resistant*	17	3	14	2	36	25	1	0	1	1	3	0
	Respiratory syncytial virus Drug-resistant	6	1	2	1	10	2	1	0	1	1	3	0

Figure 8: Overview of the number of MCM used to treat infections caused by antimicrobial-resistant priority pathogens (currently in the pipeline or in the market). Red dots indicate critical-priority pathogens, orange dots indicate high-priority pathogens and green dots indicate medium-priority pathogens. The colour coding reflects the number of available MCM, with a lighter colour indicating a smaller number and a darker colour indicating a larger number. This figure was extracted from the interim report of the study commissioned by HERA: Study on bringing AMR MCM to the market. TRL: technology readiness level.

([106]) Study on bringing AMR medical countermeasures to the market - Publications Office of the EU (europa.eu).

The following box includes a description of selected breakthroughs in antibiotic development since 2023.

- In December 2025, GARDP in collaboration with Innoviva Specialty Therapeutics, announced that the FDA has approved Nuzolvence (zoliflodacin), a first-in-class, single-dose oral antibiotic against drug-resistant *N. gonorrhoeae*, a WHO high priority pathogen ([107]).
- In April 2024, the Commission granted marketing authorisation for **Emblaveo**, a novel new antibiotic combination of aztreonam/avibactam (ATM-AVI) ([108]). Emblaveo is used in adults to treat difficult- to- treat intra-abdominal infections, hospital-acquired pneumonia, complicated infections of the urinary tract (cUTI) as well as infections due to aerobic Gram-negative bacteria in cases of limited treatment options. It has the advantage of being effective against NDM enzymes which are at increasingly prevalence in the EU.
- In March 2024, the Commission granted marketing authorisation for **Exblifep**, a new antibiotic combination of cefepime/enmetazobactam ([109]). Exblifep is used in adults to treat cUTI, hospital-acquired pneumonia and bacteraemia when it is associated or suspected to be associated with complicated urinary tract infection or hospital-acquired pneumonia.
- --In February 2024, GSK announced positive headline results from the EAGLE1 Phase 3 trial for **gepotidacin** in uncomplicated urogenital gonorrhoea. The EAGLE1 trial met its primary efficacy endpoint of non-inferiority when one compares gepotidacin with intramuscular ceftriaxone plus oral azithromycin combination therapy. In addition, in March 2025, the FDA approved gepotidacin for the treatment of uncomplicated urinary tract infections (uUTI).
- --In February 2024, the FDA rejected the new drug application for **cefepime-taniborbactam**. It requested additional chemistry, manufacturing and controls, and related data on the drug, testing methods and manufacturing process, but did not request any new clinical trials. In March, Venatorx Pharmaceuticals, a Global Antibiotic Research and Development Partnership (GARDP) collaborator, announced positive results from its pivotal Phase 3 study evaluating cefepime-taniborbactam as a treatment for hospitalised adult patients with complicated urinary tract infections, including acute pyelonephritis (i.e. kidney infections) ([110]). One trait of this antibiotic is its activity against Enterobacterales species and *P. aeruginosa* expressing serine and metallo-βlactamases.
- In December 2023, **Xacduro**, a new antibiotic combination of sulbactam/durlobactam, received the FDA's approval and is now available in the United States ([111]). This medication contains sulbactam co-packaged with

([107]) NUZOLVENCE® (Zoliflodacin) Receives U.S. FDA Approval

([108]) New antibiotic to fight infections caused by multidrug-resistant bacteria | European Medicines Agency (europa.eu).

([109]) Exblifep, INN-cefepima/enmetazobactam (europa.eu).

([110]) Venatorx Pharmaceuticals Announces Positive Results for Phase 3 Clinical Trial (CERTAIN-1) of Cefepime-Taniborbactam for Treatment of cUTI | VenatoRx Pharmaceuticals.

([111]) Sulbactam plus durlobactam: a new addition to antibacterial therapies – by Ursula Theuretzbacher – REVIVE (gardp.org).

durlobactam to offer a new treatment option for patients with infections caused by carbapenem-resistant *A. baumannii–calcoaceticus* complex (CRAb).

4.2. Non-traditional antibacterials

WHO analysis of the antimicrobial pipeline also monitors the development of various non-traditional antibacterials, which are classified into five categories: antibodies, bacteriophages and phage-derived enzymes, microbiome-modulating agents, immunomodulating agents and miscellaneous agents.

There is an increasing interest in the use of bacteriophages in the EU and beyond. In principle, there are two distinct approaches for phage therapy ([112]).

The **one-size-fits-all approach** relies on defined broad-spectrum phage cocktails that aim to target most bacteria suspected of causing a particular infectious disease. These predefined ('ready-to-use') broad-spectrum phage cocktails are developed, produced and tested within the current pharmaco-economic models, which had been designed to cater for 'static' drugs such as antibiotics. However, to be relevant for clinical practice, phage cocktails would need to contain large amounts of phages that are very difficult to produce.

Personalised phage therapy consists in the selection of one or more phages from a phage bank or from the environment and possibly adapting them (*in vitro* selection of phage mutants exhibiting increased infectivity) to more efficiently infect the bacteria isolated from the patient's infection site. Some phage therapy centres set up and maintain large therapeutic phage banks, which are regularly updated with new phage species, widening and adapting the host range to accommodate for dynamic bacterial populations. Personalised phage therapy is more elaborate and logistically complex than one-size-fits-all approaches and is less compatible with most medicinal product development and licensing pathways.

There is currently only one nationally authorised bacteriophage medicinal product in the EU (Stafal, which is authorised only in Slovakia). However, many EU Member States engage in personalised phage therapy – notably Belgium ([113]), Germany ([114]) and France ([115]).

The number of clinical trials for phage therapy products is currently limited. According to EMA, this stems mainly from two interconnected issues. Firstly, the lack of distinct regulatory and scientific guidance throughout the life cycle of such products is not helpful for potential sponsors and developers. Secondly, there is a relative paucity of clinical and manufacturing experience with phage therapy products. In addition, the use of phage therapy requires the development of specific diagnostics tools to determine their appropriate use and effectiveness.

([112]) Phage Therapy in the Year 2035- Frontiers in Microbiology. June 3 2020.
([113]) The Magistral Phage – PMC (nih.gov).
([114]) PhagoFlow | Home.
([115]) CRIOAc Lyon Phage therapy (crioac-lyon.fr).

Several initiatives are currently ongoing at EU level to support the development and assessment of phage therapy. Several key documents have been published, including (1) the 2023 EMA concept paper on the establishment of a guideline on the development and manufacture of human medicinal products specifically designed for phage therapy ([116]); (2) the 2023 EMA scientific guideline on the quality, safety and efficacy of bacteriophages as veterinary medicines ([117]); and (3) the 2024 Joint Research Centre (JRC) science for policy report ([118]) describing the advantages and disadvantages of phages for phage therapy and phage biocontrol, as well as the regulatory gaps and existing initiatives.

4.3. Antifungal agents

Four classes of antifungals are currently available: **polyenes, flucytosine, azoles** and **echinocandins**. The effectiveness of these antifungal therapies (as monotherapies or in combinations for prophylaxis, or as empiric, pre-emptive or definitive therapies) in the management of antifungal infections has plateaued ([119]).

These drugs are clinically useful, but they have several limitations (such as off-target toxicity) and drug-resistant fungi are now emerging that require additional, reserve antifungals to be developed. The analysis of the pipeline shows that progress has been made recently in developing antifungal agents, but more agents (particularly those with a broad spectrum and low toxicity) are needed. New formulations of existing antifungals are being developed to address these issues.

In April 2025, WHO published its first-ever overview and analysis of antifungal agents in clinical and preclinical development ([**Error! Bookmark not defined.**]). The landscape revealed that 9 agents are currently in clinical development against priority fungal pathogens according to the WHO's FPPL; 3 agents are in Phase 3, 2 in Phase 2 and 4 in Phase 1. Among the critical-priority pathogens, *A. fumigatus* is targeted by 6 products the highest number of antifungal candidates, with both *in vitro* and in vivo data publicly available. It is followed by *C. albicans* and *C. auris*, which are targeted by 4 and 3 agents respectively. Only 2 agents have *in vitro* and *in vivo* evidence of activity against *C. neoformans*. Overall, when one considers the key targets and the innovation needed, antifungal agents in the clinical pipeline combined with those approved in the past decade are still insufficient to address the therapeutically challenging fungal pathogens identified by the WHO.

4.4. Vaccines

Vaccines have a well-established role, both against bacterial and viral infections, as effective tools to slow the emergence and spread of AMR ([120]):

([116]) Development and manufacture of human medicinal products specifically designed for phage therapy - Scientific guideline | European Medicines Agency (EMA) (europa.eu).

([117]) Quality, safety and efficacy of bacteriophages as veterinary medicines - Scientific guideline | European Medicines Agency (EMA) (europa.eu).

([118]) Overview and outlook of phage therapy and phage biocontrol – Publications Office of the EU (europa.eu)

([119]) The antifungal pipeline: a reality check – Nature Reviews drug discovery, 12 May 2027.

([120]) The value of vaccines to mitigate antimicrobial resistance. Evidence from low- and middle-income countries, October 2023 (onehealthtrust.org).

- vaccines against bacterial infections not only avoid the use of antimicrobials which can lead to selection of resistant pathogens, but they also prevent transmission of antibiotic-resistant bacteria and reduce pathogen prevalence and its burden ([121]);
- vaccines against viral infections can indirectly fight AMR, reduce the misuse of antibiotics and preventing secondary bacterial infections (e.g. when a patient is infected with influenza viruses ([122]) or respiratory syncytial virus (RSV)).

Vaccination is an efficient strategy against community-acquired pathogens, but it is more difficult to implement in order to prevent healthcare-associated infections. Indeed, identifying high-risk patients and vaccinating them with sufficient time for immunity to develop prior to exposure is challenging.

In July 2024, GAVI, the Vaccine Alliance published its 2026-3030 strategy, which acknowledged the important contribution of vaccines to reducing AMR. This report indicates that fully scaling up *Haemophilus influenzae* type B, pneumococcal, rotavirus and typhoid vaccination in GAVI-eligible countries could reduce the use of antibiotics by over 60 million doses a year – a reduction of more than 13% ([123]). In addition, recent updates in pneumococcus vaccine with 20-valents and 21-valents indicate that they may contribute to limiting the burden of the disease and thus antibiotic consumption ([124]).

As of January 2023, only 7% of investments since 2017 have been directed towards vaccine development to combat AMR. This is three times less than the R&D funding allocated to new therapeutics to combat AMR. Vaccines against priority bacterial pathogens account for 94% of the total investment. Only 2% of vaccine R&D funding is allocated to developing vaccines against fungal infections ([125]).

In 2022, the WHO produced its first analysis of the bacterial vaccine candidates in preclinical and clinical development against drug-resistant bacteria ([126]).

The report identified four groups of pathogens with vaccine candidates in various stages of clinical development and with varying degrees of feasibility for vaccine development. Indeed, the biological feasibility of developing a vaccine depends on the bacterial pathogens considered. The feasibility is high for developing a vaccine against *Campylobacter* spp., *E. coli, H. pylori, N. gonorrhoea, Salmonella* spp. and *Shigella* spp., *In vitro* animal models for product development exist for most of these products. In contrast, developing a vaccine for pathogens that cause healthcare-associated infections (e.g. *A. baumannii*, *K. pneumoniae*, *E. faecium*, *P. aeruginosa*, *S. aureus*, *Enterobacter* spp. and *Clostridioides difficile*) is challenging. *In vitro* and animal models do exist for the development of vaccines against these pathogens, but identifying target populations in order to conduct Phase III trials is challenging.

This pipeline analysis also highlighted that, as of September 2021, there were a total of 155 candidate vaccines in active clinical (61) or preclinical development (94). Of the 61 candidate vaccines in an active status of clinical development, 10 candidate vaccines were targeting WHO critical bacteria priority pathogens. Most candidate vaccines were in

([121]) The role of vaccines in combatting antimicrobial resistance | Nature Reviews Microbiology.
([122]) Leveraging vaccines to reduce antibiotic use and prevent antimicrobial resistance: an action framework, 2020 (who.int).
([123]) Gavi: Phase VI (2026-2030)
([124]) Pfizer press release: European Commission Approves Pfizer's PREVENAR 20® to Help Protect Infants and Children Against Pneumococcal Disease, 13 March 2024.
([125]) Global AMR R&D Hub Dynamic Dashboard (globalamrhub.org).
([126]) WHO Bacterial vaccines in clinical and preclinical development 2021: an overview and analysis.

Phase 2 of development (43%; 26), while 30% (18) were in Phase 3 and 28% (17) were in Phase 1 of development. Of the total of 155 candidate vaccines, 84% (51) were for prophylactic use.

In terms of strategies for establishing priorities for prioritising vaccines development, the WHO report suggests that AMR pathogens with a low incidence may be better controlled by methods other than prophylactic vaccines. In addition, in October 2024, WHO published a report evaluating the potential role of bacterial and viral vaccines in reducing AMR. The report assessed a total of 44 vaccines that target 24 pathogens, encompassing both licensed vaccines and those in development. The report estimates the potential impact of these vaccines on AMR-related health outcomes, antibiotic use and economic costs; and provides a detailed modelling of the burden averted by vaccines and the feasibility of development for each pathogen ([127]).

4.5. Diagnostics

The use of diagnostics in the AMR context serves several important purposes – including accurately identifying the specific pathogen responsible for an infection and determining the susceptibility of the identified pathogen to various antimicrobials (known as antimicrobial susceptibility testing (AST)). The use of diagnostics enhances antimicrobial treatment and facilitates appropriate infection-control measures in healthcare settings to prevent the spread of infections with AMR pathogens.

Host defence and biomarkers detection assays identify biomarkers and host responses associated with infection, thus providing a different approach to diagnosing infections. For example, blood tests for C-reactive protein (CRP) and Procalcitonin (PCT) are rapid, easy-to-use diagnostic tests that can be used at the point of care. The CRP test is used to detect a non-specific, inflammatory-related protein that increases with bacterial infections. PCT is another biomarker positive for bacterial infection and sepsis. Host-response assays could help in initially determining whether an infection is bacterial or non-bacterial and guide the appropriate use of antimicrobials. However, none of these tests perform AST or can identify the specific pathogen that is causing the infection. These tests also require further development to improve their accuracy and reliability in diagnosing infections accurately.

AST methods can be divided into two main approaches: (1) phenotypic methods that directly assess the growth of pathogens in the presence of the antimicrobial under investigation (e.g. via disc diffusion); and (2) genotypic methods that identify genetic markers associated with AMR (for example, via whole genome sequencing – WGS). Newer technologies (e.g. WGS, loop-mediated isothermal amplification and digital PCR) are beginning to add a new layer of sophistication to susceptibility-profiling, offering the promise of more comprehensive or faster analysis. However, some issues need to be addressed before they can be adopted. For example, the JRC has investigated the challenges associated with using WGS for AMR-monitoring, including the lack of standardised bioinformatics pipelines, infrastructure limitations in many regions and the

([127]) Estimating the impact of vaccines in reducing antimicrobial resistance and antibiotic use: technical report.

high volume of data generated ([128],[129],[130]). A roadmap to address these issues involves building local capacity, improving data-sharing and interoperability, and integrating WGS with existing surveillance systems. [131]

Mapping AMR diagnostics on the market and in development is very challenging, particularly ([132]) because there are significant information gaps in the absence of a centralised database. The WHO published its first-ever landscape analysis on commercially available and pipeline *in vitro* diagnostics for fungal diseases in April 2025 (**Error! Bookmark not defined.**). This analysis shows that, while commercially available tests exist for fungal priority pathogens, they rely on well-equipped laboratories and trained staff – so most people in LMICs do not benefit from them. There is an urgent need for faster, more accurate, affordable and user-friendly diagnostic solutions for a broad range of fungal pathogens. This includes tests that can be used at or near the point-of-care, particularly in regions where resources are limited. The WHO is currently working on a landscape analysis of bacterial diagnostics.

In January 2023, HERA published a study on bringing AMR MCM to the market ([133]), including an analysis of products on the market and in development. Regarding bacterial diagnostics, the study showed that most of the products on the market use non-phenotypic methods (primarily amplification-based methods) and immunoassays. The remaining diagnostic methods are automated/semi-automated phenotypic testing methods.

Figure 6: Types of diagnostic devices available on the market today. Extracted from the HERA study on bringing MCM to the market.

([128]) Angers-Loustau A., Petrillo M.., et al., *The Role and Implementation of Next-Generation Sequencing Technologies in the Coordinated Action Plan against Antimicrobial Resistance*, Publications Office of the European Union, 2017, https://dx.doi.org/10.2760/745099.

([129]) Angers-Loustau A., Petrillo M., et al., *The challenges of designing a benchmark strategy for bioinformatics pipelines in the identification of antimicrobial resistance determinants using next generation sequencing technologies*, 2018, https://doi.org/10.12688/f1000research.14509.2.

([130]) Petrillo M., Fabbri M., et al., *A roadmap for the generation of benchmarking resources for antimicrobial resistance detection using next generation sequencing*, 2021, https://doi.org/10.12688/f1000research.39214.2.

([132]) Petrillo M., Fabbri M., et al., *A roadmap for the generation of benchmarking resources for antimicrobial resistance detection using next generation sequencing*, 2021, https://doi.org/10.12688/f1000research.39214.2.

([133]) Study on bringing AMR medical countermeasures to the market – Publications Office of the EU (europa.eu).

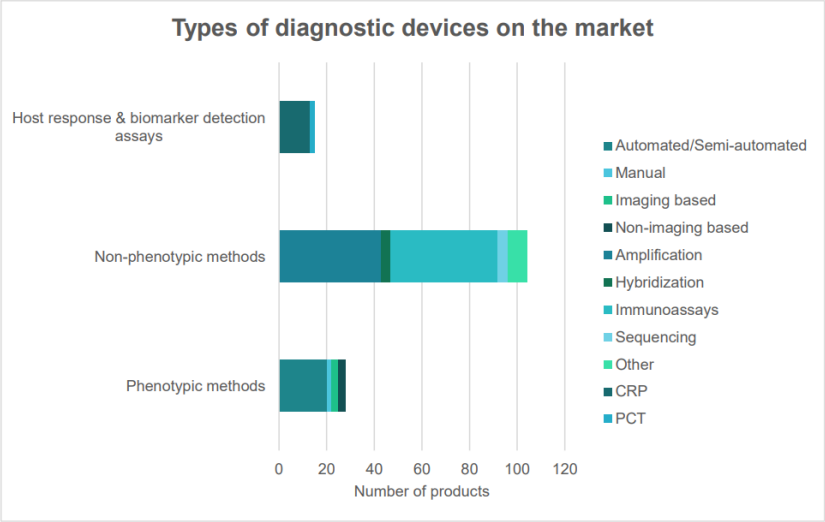

Figure 26: Types of diagnostic devices available on the market today

Most diagnostic solutions on the market perform either differential diagnosis (e.g. distinguish a bacterial from a viral infection) or species identification (82% and 83% respectively). Only a small proportion of these solutions can perform AST (only 15%). Most diagnostic devices (65%) can produce results in under two hours. However, only 38% of the AST diagnostic devices on the market can produce results in under two hours.

Classical culture-based phenotypic methods for pathogen identification and AST methods provide gold-standard results, but they are still relatively slow (despite the introduction of automated and semi-automated methods which have reduced the time-to-result). Non-phenotypic methods on the market (e.g. genotypic characterisation for AMR) are often faster and simpler methods for carrying out pathogen identification and/or AST/resistance testing. However, the correspondence between phenotypic and genotypic results is not always clear, and direct and non-phenotypic methods often require advanced laboratory settings.

These results suggest a gap in rapid AST solutions that can indicate in under two hours which antimicrobial will be effective against a particular drug-resistant pathogen. Rapid AST methods can reduce AMR by enabling timely, targeted treatments that minimise the unnecessary use of broad-spectrum antibiotics.

Diagnostic devices that carry out rapid AST and produce results in under two hours are in development, but they are not point-of-care tests and are therefore less efficient in preventing inappropriate use of antimicrobials. Furthermore, most diagnostic methods aim to identify drug-resistance determinants of multidrug-resistant pathogens but the most urgent clinical need for patients and physicians is rather to determine which (narrow-spectrum) drug is effective against the pathogen in question ([134]). Few studies have explored whether there are any drug-susceptible determinants (e.g. particular genetic mutations, absence of resistance genes or intact antibiotic target sites) or other multiomics traits (characteristics inferred from the integration and bioinformatic analysis of data from genomics, transcriptomics, proteomics, etc.) in AMR strains. These drug-susceptible feature data are very valuable because they can be used for model-training in machine

([134]) Frontiers | Paving the way for precise diagnostics of antimicrobial-resistant bacteria (frontiersin.org).

learning and for the development of molecular-based assays that can directly detect drug-susceptible markers. More innovative efforts are needed in this area in the future.

5. PRIORITY AMR PATHOGENS FOR THE EU

This section provides a summary of the available intelligence on (1) the bacterial pathogens that the WHO considers to be of a critical and high priority; and (2) the fungal pathogens associated with a critical priority.

The main attributes of each AMR priority pathogen (including health burden, incidence and trends in the EU) are summarised in **Error! Reference source not found.** and detailed for each pathogen in individual sections.

5.1. General overview

In the EU, the top 3 pathogens in terms of **health burden** as measured in DALYs and attributable deaths were:

- third-generation cephalosporin-resistant *E. coli*;
- MRSA;
- third-generation cephalosporin-resistant *K. pneumoniae*.

These three pathogens together represented 58% of the EU health burden. Another 31% of the total burden resulted from infections with carbapenem-resistant bacteria (including carbapenem-resistant *K. pneumoniae*, *Acinetobacter* spp. and *P. aeruginosa*). EU targets for these three resistant pathogens exist under the 2023 Council Recommendation, see section 3.4 of this document.

In terms of trends, the most concerning increases in the incidence of bloodstream infections reported by EU/EEA countries between 2019 and 2023 ([135]) were observed for:

- carbapenem-resistant *K. pneumoniae* (+57.5%);
- vancomycin-resistant *E. faecium* (+24.3%);
- third-generation cephalosporin-resistant *K. pneumoniae* (+21.9%);
- carbapenem-resistant *Acinetobacter spp*. (+21.6%).

At global level, six pathogens associated with resistance had an attributable AMR burden of at least 100 000 attributable deaths in 2021 ([136]). During the reporting period, the pathogen-drug combination with the largest increase in attributable burden globally was MRSA, which caused 130 000 attributable deaths in 2021. **In terms of trends**, the drug-pathogen combinations of concern were MDR tuberculosis, carbapenem-resistant *A. baumannii,* carbapenem-resistant *K. pneumoniae* and third-generation cephalosporin-resistant *K. pneumoniae* ([137]).

([135]) Antimicrobial resistance in the EU/EEA, Annual Epidemiological Report for 2023, EARS-Net.
([136]) in descending order, *S. aureus, A. baumannii, E. coli, K. pneumoniae, S. pneumoniae and P. aeruginosa*
([137]) Global burden of bacterial antimicrobial resistance 1990–2021: a systematic analysis with forecasts to 2050 – The Lancet.

Table 2: Overview table of AMR priority pathogens

Pathogen	EU surveillance	EU 2030 target on incidence*	EU attributable deaths**	EU DALY	Incidence in the EU/EEA***	Trend****	Vaccine availability, WHO AMR vaccine feasibility category	WHO rate level of treatability
Escherichia coli, third-generation cephalosporin-resistant	EARS-Net	**9.67**	9 079	216 440	10.35[II]	- 3.6%	No, group B	Medium
Klebsiella pneumoniae, third-generation cephalosporin-resistant	EARS-Net	-	4 714	145 761	9.25[II]	+ 21.9%	No, group C	Medium
Klebsiella pneumoniae, carbapenem-resistant	EARS-Net	**2.39**	4 076	123 253	3.97[I]	+ 57.5%	No, group C	Medium-low
Acinetobacter baumannii, carbapenem-resistant	EARS-Net	-	3 656	119 107	2.98[I]	+ 21.6%	No, group D	Low
Escherichia coli, carbapenem-resistant	EARS-Net	-	157	4 199	0.14[I]	- 30%	No, group B	Medium
Staphylococcus aureus, methicillin-resistant	EARS-Net	**4.79**	6 463	170 581	4.64	- 17.6%	No, group D	High
Enterococcus faecium, vancomycin-resistant	EARS-Net	-	3 414	87 375	2.30	+ 24.3%	No, group D	Medium
Pseudomonas aeruginosa, carbapenem-resistant	EARS-Net	-	3 210	107 511	2.01[I]	+16.2%	No, group D	Medium-low
Neisseria gonorrhoeae, fluoroquinolone and/or third-generation cephalosporin-resistant	EU-GASP	-	N/A	N/A	N/A	Increase	No, group B	Medium-low
Shigella, fluoroquinolone-resistant	TESSy	-	N/A	N/A	N/A	N/A	No, group C	High-medium
Salmonella typhi, fluoroquinolone-resistant	TESSy	-	N/A	N/A	N/A	N/A	Yes, group A	Medium-low
Non-typhoidal *Salmonella,* fluoroquinolone-resistant	Zoonose Net	-	N/A	N/A	N/A	Increase[V]	No, group C	High-medium
Mycobacterium tuberculosis, rifampicin-resistant and multidrug-resistant	TESSy	-	117	N/A	0.2	+ 0.2%	Yes, group A	Low
Aspergillus fumigatus	Not notifiable	-	N/A	N/A	N/A	N/A	No	N/A
Cryptococcus neoformans	Not notifiable	-	N/A	N/A	N/A	N/A	No	N/A
Candida albicans	Not notifiable [IV]	-	N/A	N/A	N/A	N/A	No	N/A
Candidozyma auris	Not notifiable	-	N/A	N/A	N/A	N/A	No	N/A

For each pathogen, the table presents the corresponding surveillance network, EU target for incidence reduction in 2030, EU/EEA health burden in deaths and disability-adjusted life years (DALY), incidence and trends in the EU/EEA, vaccine availability, vaccine feasibility classification by the WHO and the rate level of treatability according to the WHO. Pathogens highlighted in red and orange correspond to the BPPL and FPPL critical and high-priority groups respectively. N/A stands for non-applicable. TESSy: The European Surveillance System

* The European Union specific targets to reduce the incidence of certain AMR infections per 100 000 population by 2030.

In 2020 (according to the ECDC report on the health burden of AMR 2016-2020, including all *Acinetobacter* species (Error! Bookmark not defined.**)) and in 2023 (according to the ECDC and WHO Europe Tuberculosis surveillance and monitoring in Europe 2025-2023 (**Error! Bookmark not defined.**)).

*** The incidence in the EU/EEA is showed for 2023 (number per 100 000 population) as according to the EARS-Net 2023 report, including all *Acinetobacter* species (**Error! Bookmark not defined.**), and according the ECDC and WHO Europe Tuberculosis surveillance and monitoring in Europe 2025-2023 (**Error! Bookmark not defined.**).

**** in 2023 in comparison with 2019 as the baseline year.

[I] imipenem/meropenem resistance.

[II] cefotaxime/ceftriaxone/ceftazidime resistance.

[IV] (Bloodstream infections are notifiable via the WHO Global Antimicrobial Resistance and Use Surveillance System (GLASS)).

[V] https://www.ecdc.europa.eu/sites/default/files/documents/SALM_AER_2022_Report.pdf.

5.2. Bacterial pathogens from the 'critical group' of the WHO BPPL 2024

5.2.1. Carbapenem-resistant *Acinetobacter baumannii* (CRAB)

A. baumannii was one of the leading pathogens in the world for deaths associated with resistance, with more than 100 000 attributable deaths in 2021 (**Error! Bookmark not defined.**). Carbapenem-resistant *A. baumannii* was also listed as a drug-pathogen combination of concern due to increasing trends.

In the EU/EEA, in 2020, the estimated number of deaths attributable to carbapenem-resistant *Acinetobacter* spp. increased over the previous four years to 3 656 ([138]). With regard to the incidence, based on the information available in the EARS-Net 2023 report, there was a decrease in the number of isolates and the mean-resistance percentages for invasive infections caused by *Acinetobacter* spp. (primarily the *A. baumannii* complex) in the EU/EEA in 2022 (including CRAB) compared with 2021. This suggests that specific control interventions in affected hospitals may have had some positive impact. However, when examining the broader trend, the incidence of CRAB in the EU has increased by 21.6% compared with the baseline year of 2019 (see Table 1).

CRAB is one of the two pathogens (together with RR-TB) that is associated with the lowest level of treatability according to the WHO's BPPL prioritisation (see **Error! Reference source not found.**). Current treatment options for CRAB are limited ([139]). Inherent and acquired resistance mechanisms, as well as host factors, significantly restrict options for treatment. Despite its significant nephrotoxicity, colistin is considered a primary treatment and is often used in combination with other antimicrobials, such as tigecycline, ampicillin-sulbactam, meropenem or fosfomycin. New drugs such as durlobactam and cefiderocol have shown considerable therapeutic potential against CRAB and may be used as salvage treatment.

There is currently no vaccine available or in clinical development against *A. baumannii* infection, but there are vaccines in preclinical development. However, developing a vaccine against this pathogen is considered challenging because *A. baumannii* is classified in Group D under the WHO's AMR vaccine feasibility classification (**Error! Bookmark not defined.**) (i.e. pathogens which currently have low feasibility for vaccine development).

5.2.2. *Carbapenem-resistant Enterobacterales (CRE) and third-generation cephalosporin-resistant Enterobacterales (C3GRE)*

K. pneumoniae and *E. coli* were among the world's leading pathogens for deaths associated with resistance, with more than 100 000 attributable deaths in 2021 (**Error! Bookmark not defined.**). Additionally, carbapenem-resistant *K. pneumoniae* and third-generation cephalosporin-resistant *K. pneumoniae* were listed as antimicrobial-resistant pathogens of concern due to increasing trends.

In the EU/EEA, in 2020, the estimated number of deaths attributable to carbapenem-resistant *E. coli* and carbapenem-resistant *K. pneumoniae* was 157 and 4 076 respectively. The estimated number of deaths attributable to C3GR *E. coli* and C3GR *K. pneumoniae* was 9 079 and 4 714 respectively.

With regard to incidence, based on the information available in the EARS-Net 2023 report, the estimated incidence of bloodstream infections with carbapenem-resistant *K. pneumoniae* in 2023 showed an increase of almost 57.5% by comparison with the 2019

([138]) Revised estimates of burden of disease for antimicrobial resistance.
([139]) Treatment of infections caused by carbapenem-resistant Acinetobacter baumannii – PMC.

baseline year (Table 1). This increasing trend is of considerable concern and presents significant challenges in achieving the EU 2030 targets for AMR. In the case of carbapenem-resistant *E. coli*, the incidence in 2023 decreased by 30% compared with the 2019 baseline year.

The percentage of bloodstream infections due to third-generation cephalosporin-resistant *E. coli* decreased by 3.6% compared with the 2019 baseline year. However, the 2023 incidence remains higher than the EU 2030 target for AMR. The incidence of bloodstream infections due to third-generation *K. pneumoniae* had increased by 21.9% since the 2019 baseline year.

In addition to the regular surveillance, the ECDC carried out ad hoc assessments of specific AMR health events. With regard to bloodstream infections in 2023, the ECDC reported a significant increase in *E. coli* isolates with the antimicrobial-resistant gene $bla_{\text{NDM-5}}$, suggesting a rapid global and EU/EEA expansion of these multidrug-resistant strains ([140]) that had probably been exacerbated by international travel. The co-existence of resistance to other antibiotics alongside the antimicrobial-resistant gene $bla_{\text{NDM-5}}$ poses a severe threat to public health because it limits treatment options. In November 2023, another report detailed the swift spread of carbapenemase-producing *K. pneumoniae* ST39 in Greece ([141]), emphasising the need for routine molecular surveillance to track and manage AMR threats effectively.

On 3 February 2025, an ECDC rapid risk assessment highlighted an increase in carbapenem resistance in Enterobacterales (e.g. *K. pneumoniae* and *E. coli*) that poses a significant threat to patients and healthcare in the EU/EEA ([142]). The assessment was followed by the adoption of an opinion of the Health Security Committee on rapidly increasing incidence of CRE in healthcare settings on 13 May 2025. The opinion seeks to address, through recommended targeted measures, the public health challenge of rapidly rising CRE, especially in healthcare settings, notwithstanding and complementary to other existing and overarching initiatives on AMR through a One Health approach ([143]). Carbapenem-resistant Enterobacterales are classified as part of the critical-priority group in the WHO's BPPL.

Treatment options for CRE and C3GRE depend on the type of carbapenemase enzyme types they produce. In both cases, therapeutic decisions are further guided by infection severity and antimicrobial susceptibility testing. According to the WHO's BPPL, CRE and C3GRE are associated with a medium-low and medium treatability respectively. Some of the options for CRE are meropenem/vaborbactam, imipenem-cilastatin-relebactam and cefiderocol. The treatment options for C3GRE include carbapenems, ceftazidime-avibactam, cefiderocol and fosfomycin. Last-resort options for the treatment of these resistant pathogens include colistin. While its use is associated with significant toxicity, it may still be recommended when no other alternatives are available). There are several agents in development (including agent cefepime-taniborbartam, cefepime-zidebactam and cefepime-nacubactam) which are active against both the CRE and C3GRE pathogens.

([140]) ECDC surveillance report: Increase in Escherichia coli isolates carrying blaNDM-5 in the European Union/European Economic Area, 2012–2022, 11 May 2023.

([141]) Rapid spread of highly drug-resistant Klebsiella pneumoniae in Greek hospitals – ECDC, 24 November 2023.

([142]) Rapid risk assessment - Carbapenem-resistant Enterobacterales – third update.

([143]) Opinion of the Health Security Committee on rapidly increasing incidence of carbapenem-resistant Enterobacterales (CRE) in healthcare settings – European Commission.

No approved vaccine exists yet for extraintestinal *E. coli* or *K. pneumoniae*. They are classified in group C under the WHO's vaccine feasibility classification (**Error! Bookmark not defined.**) because some candidates have been identified in early clinical trials.

5.2.3. Rifampicin-resistant tuberculosis (RR-TB)

The WHO's 2023 Global Tuberculosis Report highlights that TB remains one of the leading infectious killers (particularly among people with HIV) and is a significant contributor to AMR-related deaths ([144]). In 2024, WHO added RR-TB in its bacterial priority pathogen list, after an independent analysis with parallel criteria and subsequent application of an adapted multicriteria decision analysis matrix showed that RR- TB remained among the top- ranked resistant pathogens requiring urgent attention for research, development, and public health action.

Globally, the TB incidence rate increased by 1.9% from 2020 to 2022, partly due to COVID-19 disruptions ([145]). The estimated annual number of people who developed MDR/RR-TB was relatively stable between 2020 and 2022 (following a slow downward trend between 2015 and 2019), but MDR and XDR-TB continue to pose an important threat. There were an 410 000 estimated MDR/RR-TB cases in 2022, but patients only receive treatment in approximately 40% of these cases.

In 2023, 38 993 cases of TB were reported in 29 EU/EEA countries ([146]). Cases increased by approximately 5.41% between 2021 and 2023, but the overall notification rate in most countries has continued to decrease over the last five years. The total number of 38 993 cases included 19 170 cases with drug susceptibility testing results for at least rifampicin. 814 (4.7%) of these 19 170 cases involved MDR-TB. 155 cases (27.6%) of the 561 RR/MDR-TB cases that were tested for fluoroquinolone susceptibility were classified as pre-XDR-TB (i.e. they were resistant to rifampicin and at least one other drug but were not yet fully XDR-TB cases). 150 cases (96.8%) of these 155 pre-XDR-TB cases were also tested for susceptibility to any other Group A drug and 15 cases (10.0%) of these met the XDR-TB definition. 56.3% (About 324) of the 577 RR/MDR-TB cases notified in 2021 with a treatment outcome reported in 2023, were treated successfully, 17.3% died (100 deaths) and 8% (46) experienced treatment failure (the rest were either not evaluated or were still on treatment). Of the 79 cases categorised as pre-XDR-TB, notified in 2021 and reporting a treatment outcome at 24 months in 2023, 37 cases were reported as having been treated successfully (46.8%), 17 (21.5%) were reported to have died, 14 (17.7%) had experienced treatment failure, 3 (3.8%) were lost to follow-up, 4 (5.1%) were still on treatment and 4 (5.1%) had not been evaluated.

RR-TB is one of the two pathogens (together with CRAB) associated with the lowest level treatability according to the WHO's BPPL prioritisation (see **Error! Reference source not found.**). Since 2022, the WHO has endorsed the use of a new all-oral six-month regimen composed of bedaquiline, pretomanid, linezolid and moxifloxacin (BPaL(M)) in people suffering from MDR/RR-TB. In 2023, 23 of the 44 (52.3%) countries in the WHO's Europe

([144]) Global tuberculosis report 2023 (who.int)
([145]) WHO Global Tuberculosis report 2023. TB incidence

([146]) https://www.ecdc.europa.eu/sites/default/files/documents/TB-2025-Surveillance-report.pdf.

region had access to all the drugs composing the BPaL(M) regimen ([147]). As reflected in the WHO's antibacterial pipeline analysis between 1 November 2023 and 31 December 2023, 19 agents are being developed against drug-resistant *M. tuberculosis* (2 in Phases 2/3 and 3 respectively).

The only licensed vaccine for TB prevention is the Bacillus Calmette-Guérin (BCG) vaccine, which is based on the attenuation of *Mycobacterium bovis* that was originally isolated from cattle ([148]) and was first administered over a century ago. The WHO recommends its use at birth in countries with an incidence higher greater than 10 TB cases per 100, 000 population per year. The vaccine has an efficacy rate of 60–80% against meningeal and miliary TB, which are disseminated and aggressive forms of the disease that occur during childhood. It and has been shown to protect against TB for up to 10–15 years post-vaccination. However, clinical trials have shown variable efficacy in preventing pulmonary forms, (the transmissible form of the disease), especially in adolescents and adults.

The vaccine has not been compulsory in several EU Member States in recent years, but it is still strongly recommended for people at risk of exposure to tuberculosis and those living in at-risk areas, where tuberculosis still circulates ([149]).

M. tuberculosis is considered as group A (very high pipeline feasibility) under the WHO's AMR vaccine feasibility classification (**Error! Bookmark not defined.**). In August 2023, there were 16 vaccine candidates in clinical trials ([150]): 4 in Phase I, 8 in Phase II and 4 in Phase III. They included candidates to prevent TB infection and TB disease, and to enhance treatment outcomes for those already affected by TB.

5.3. Bacterial pathogens from the 'high group' of the WHO BPPL 2024

5.3.1. Vancomycin-resistant Enterococcus faecium

Determining the exact global mortality figures attributed specifically to vancomycin-resistant *Enterococcus faecium* (VREfm) is challenging due to limited comprehensive data. However, studies indicate that BSIs caused by VREfm are associated with significant mortality rates. In the EU/EEA, an estimated 3 414 deaths were attributable to VREfm in 2020 (**Error! Bookmark not defined.Error! Bookmark not defined.**). Based on information available from the EARS-NET 2023 report, the estimated incidence of VREfm isolates from bloodstream infections (per 100 000 population) was 2.30 in 2023 (**Error! Bookmark not defined.**). In terms of trends, the incidence of VREfm bloodstream infections in 2023 was 24.3% higher than in the 2019 baseline year.

Treatment of VREfm is associated with a medium level of treatability according to the WHO's BPPL prioritisation. Treatment options include the use of linezolid and

([147]) Availability of drugs and resistance testing for bedaquiline, pretomanid, linezolid, and moxifloxacin (BPaL(M)) regimen for rifampicin-resistant tuberculosis in Europe - PubMed.

([148]) Calmette A., Guerin C. and Weill-Halle B., 'Essai d'immunisation contre l'infection tuberculeuse', *Bulletin de l'Académie Nationale de Médecine*
., Vol. 91, 1924, pp. 787–96.d42859-020-00010-x.pdf

([149]) Vaccine Scheduler | ECDC.

([150]) MTBVAC: A Tuberculosis Vaccine Candidate Advancing Towards Clinical Efficacy Trials in TB Prevention.

daptomycin. There are several agents in development, including alternatives to antibiotics such as the use of phage therapy and immunotherapy with monoclonal antibodies ([151]).

There are currently no available vaccines or vaccine candidates in preclinical or clinical trials against *E. faecium*. This pathogen is classified in Group D under the WHO's AMR vaccine categorisation (i.e. pathogens which currently have low feasibility for vaccine development (**Error! Bookmark not defined.**)).

5.3.2. Carbapenem-resistant Pseudomonas aeruginosa

Globally, in 2021, the total deaths attributable to AMR of carbapenem-resistant *Pseudomonas aeruginosa* (CRPA) were 456,00 [(70)]

In the EU/EEA, an estimated 3 210 deaths were attributable to CRPA in 2020 (**Error! Bookmark not defined.**). The incidence of bloodstream infections with CRPA increased by 16.2% on the 2019 baseline year (based on the information available in the EARS-Net 2023 report) (**Error! Bookmark not defined.**).

CRPA has been associated with a medium-low level of treatability according to the WHO's BPPL prioritisation. (Figure 2). Treatment of CRPA includes the use of beta-lactam-based therapies such as meropenem/vaborbactam and cefiderocol. Several agents are in development, such as the cefepime-taniborbartam agent (**Error! Bookmark not defined.**).

No vaccine candidate has been identified in clinical development for *P. aeruginosa* and vaccine development feasibility is low (classified in Group D under the WHO's AMR vaccine feasibility classification). Four active *P. aeruginosa* vaccine candidates are in the later stages of preclinical development. These use a range of technologies, including the MAPS platform, phage-based vaccine, a live-attenuated Salmonella strain and an inactivated whole cell vaccine. In addition, several promising vaccine candidates were identified at earlier stages of preclinical development (**Error! Bookmark not defined.**).

5.3.3. Methicillin-resistant Staphylococcus aureus (MRSA)

Globally, MRSA was the pathogen-drug combination with the largest increase in attributable burden in all age groups in 1990-2021, when 130 000 deaths were directly attributable to infections caused by this pathogen.

In the EU/EEA, an estimated 6 463 deaths were attributable to MRSA infections in 2020. Based on the information available in the EARS-Net 2023 report, there was a 17.6% decrease in bloodstream infections caused by this pathogen by comparison with the 2019 baseline year, thus achieving the EU 2030 targets for AMR.

Treatment of MRSA depends on the severity and location of the infection. MRSA is associated with a high level of treatability according to the WHO's BPPL prioritisation. Vancomycin and daptomycin are the agents of choice for the treatment of invasive MRSA infections. Alternative agents that might be used for second-line therapy include telavancin, ceftaroline and linezolid. There are agents in development including zoliflodacin (a new antibiotic class).

S. aureus is in Group D of the WHO's AMR vaccine feasibility group classification. This group contains pathogens with only a few or no vaccine candidates in the pipeline and low vaccine development feasibility There are currently 12 active preclinical vaccine

([151]) Wei et al., 'Enterococcus faecium: evolution, adaptation, pathogenesis and emerging therapeutics', *Nat Rev Microbiol*, No 22, 2024, pp. 705–721.

candidates against *S. aureus*. 2 vaccine candidates are in clinical development. No licensed vaccines exist to prevent *S. aureus* infections (**Error! Bookmark not defined.**).

5.3.4. Fluoroquinolone and/or third-generation cephalosporin-resistant *Neisseria gonorrhoeae*

In June 2024, ECDC published a report underlining the threat of increasing AMR in *N. gonorrhoeae* ([152]). 23 European countries submitted 4 396 isolates from patients diagnosed with gonorrhoea to the Euro-GASP. The proportion of isolates resistant to azithromycin increased significantly to 25.6% from 14.2% in 2021. The fact that azithromycin is often used with ceftriaxone to treat gonorrhoea makes this finding particularly concerning. Resistance to the fluoroquinolone ciprofloxacin had also increased – 65.9% of isolates were exhibiting resistance in 2022 (up from 62.8% in 2021). Resistance to cefixime remains low at 0.3%, but continuing monitoring is crucial, particularly because gonococcal strains resistant to cefixime and ceftriaxone are spreading internationally. In addition, sporadic cases of XDR and MDR gonorrhoea strains have been reported in the EU/EEA ([153, 154]).

The WHO's BPPL rates the level of treatability of fluoroquinolone-resistant and third-generation cephalosporin-resistant *N. gonorrhoeae* as medium and medium/low respectively. The 2020 European guideline for the diagnosis and treatment of gonorrhoea in adults ([155]) sets out recommendations for the treatment of gonorrhoea. For ceftriaxone-resistant gonorrhoea, the guidelines recommend treatment with dual therapy that includes combination of azithromycin with ceftriaxone, spectinomycin or gentamicin. Two new treatments have recently shown positive results in Phase III clinical trials: zoliflodacin and gepotidacin, both of which have the potential to treat resistant gonorrhoea infections. These agents represent a breakthrough in antibiotic development because they belong to two new classes of antibiotics with each having a distinct mode of action. *N. gonorrhoeae* is included in Group B of the WHO's AMR vaccine feasibility group classification (i.e. pathogens with vaccines that are in late-stage clinical trials with high development feasibility).

Currently, no vaccine is specifically approved for *N. gonorrhoeae.* However, the MenB vaccine (4CMenB, Bexsero), which was originally developed for meningitis B, provides about 30–41% protection against gonorrhoea. In June 2025, Galicia (Spain) became the first region to introduce a gonorrhoea vaccination programme, targeting adults aged 18–65 years at high risk of sexually transmitted infections – including people using pre-exposure or post-exposure prophylaxis and those with recent or recurrent diagnoses of gonorrhoea, chlamydia, syphilis, mpox or HIV ([156]).

In August 2025, the UK launched the world's first national gonorrhoea vaccination programme, offering two doses of 4CMenB through sexual health services to high-risk

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([152]) Antimicrobial resistance in gonorrhoea: Rising threat to treatment efficacy (europa.eu).
([153]) Eurosurveillance | Two cases of extensively drug-resistant (XDR) Neisseria gonorrhoeae infection combining ceftriaxone-resistance and high-level azithromycin resistance, France, November 2022 and May 2023.
([154]) Eurosurveillance | Multidrug-resistant Neisseria gonorrhoeae isolate SE690: mosaic penA-60.001 gene causing ceftriaxone resistance internationally has spread to the more antimicrobial-susceptible genomic lineage, Sweden, September 2022.
([155]) 2020 European guideline for the diagnosis and treatment of gonorrhoea in adults – PubMed.
([156]) The Lancet, Galicia's gonorrhoea vaccination programme, November 2025.

men who have sex with men. In addition, there is one vaccine candidate in clinical development (Phase 3) and several candidates in late-stage preclinical development (**Error! Bookmark not defined.**).

5.3.5. Fluoroquinolone-resistant Shigella

Shigella is a major cause of diarrhoeal disease globally but particularly affects vulnerable populations in low-resource settings. Unfortunately, the EU-level surveillance data for shigellosis do not allow inference regarding the presence of AMR in the EU/EEA ([157]). However, a substantial proportion of the isolates tested in 2022 were resistant to ampicillin and ciprofloxacin.

In 2023, the ECDC published an epidemiological update on the spread of multidrug-resistant *Shigella* in the EU/EEA among gay, bisexual and other men who have sex with men (gbMSM) ([158]). Between April and July 2023, over 300 shigellosis cases (many with MDR *Shigella sonnei* infections) were reported to the ECDC. An increase in XDR *Shigella sonnei* infections among gsMSM was already noted in 2020−2022.

The WHO's BPPL rates the level of treatability of fluoroquinolone-resistant *Shigella* as high/medium. Resistance to first-line treatments such as fluoroquinolones limits the available effective treatment for severe disease to intravenous, last-resort antimicrobials agents, such as carbapenems. ShigActive, a phage cocktail that is currently in Phase 1/2a, has been investigated for the treatment of shigellosis.

Shigella spp. belongs to Group C of the WHO's vaccines feasibility classification, which includes pathogens with vaccine candidates either in early clinical trials or with moderate to high feasibility of vaccine development. There is currently no available vaccine for *Shigella* spp., but eight vaccine candidates are in active clinical trials (**Error! Bookmark not defined.**). Vaccines for this pathogen have been a longstanding area of research, but progress has been slow due to the complexity of developing an effective and safe vaccine.

5.3.6. Fluoroquinolone-resistant *Salmonella* spp.

Typhoidal salmonellas belong to *Salmonella enterica* subsp. enterica serovars typhi, paratyphi A, B and C. They are human host-adapted organisms that cause typhoid and paratyphoid fever. Non-typhoidal Salmonella strains include all other serovars within the subspecies enterica. They can either infect a multitude of animal hosts or be host-specific for particular animal species.

The overall global burden of Salmonella infections is high but differs between regions. Whereas typhoid fever is most prevalent in south and south-east Asia, non-typhoidal salmonellosis is prevalent across the globe and associated with mild gastroenteritis. By contrast, invasive non-typhoidal Salmonella causes bloodstream infections associated with high mortality, particularly in sub-Saharan Africa.

5.3.6.1. Fluoroquinolone-resistant *Salmonella typhi*

Typhoid fever predominantly affects impoverished communities with limited access to adequate water, sanitation and hygiene infrastructure. Each year, an estimated 10 million

([157]) ECDC Surveillance Report – Shigellosis – Annual epidemiological report for 2022.
([158]) ECDC, Epidemiological Update Spread of multidrug-resistant Shigella in EU/EEA among gay, bisexual and other men who have sex with men, July 2023.

cases and approximately 116, 800 deaths are attributed to typhoid fever (**Error! Bookmark not defined.**).

Fluoroquinolone-resistant *Salmonella typhi* (*S. typhi*) is a major public health issue in areas where typhoid fever is endemic. A large-scale emergence and spread of XDR *S. typhi* (resistant not only to fluoroquinolones but also to chloramphenicol, ampicillin, trimethoprim-sulfamethoxazole and third-generation cephalosporins) has been reported since 2016 in Pakistan.

In the EU/EEA, typhoid fever is relatively rare and is mainly acquired during travel to countries outside the EU/EEA, particularly in South Asia. In 2020, 17 EU/EEA countries reported a total of 315 cases (including paratyphoid fever). Resistance to ciprofloxacin was observed in 69.6% of isolates. 6 isolates from 5 EU/EEA countries displayed the same resistance pattern as the XDR *S. Typhi* in the outbreak which has been ongoing in Pakistan since 2016.

Typhoid infections can cause very severe disease. Case fatality rates in untreated cases of typhoid fever can reach 26%. In 2020, 70% of the cases reported in the EU were associated with a bloodstream infection. In such cases, antimicrobial treatment is necessary in order to avoid worsening symptoms, including fatality. The WHO's BPPL categorises the treatability of fluoroquinolone-resistant typhoidal Salmonella as medium/low (Figure 2), indicating little availability of qualitative antibiotic options for treatment of infection by this pathogen. Azithromycin, third-generation cephalosporins and carbapenems are the alternative options for fluoroquinolone-non-susceptible infections.

Vaccines against typhoid fever are nationally authorised in all EU Member States for pre-exposure prophylaxis ([159]). Two types of vaccines are available: the oral live-attenuated vaccine (Ty21a) three-dose regimen (Vivotif) and the purified Vi polysaccharide vaccine, which is given intramuscularly (Typhim Vi). The WHO has recommended these vaccines since 2008 for the control of typhoid in endemic and epidemic settings ([160]). In addition, typhoid vaccination should be considered for travellers to typhoid-endemic areas.

5.3.6.2. Fluoroquinolone-resistant non-typhoidal *Salmonella*

Non-typhoidal Salmonella causes gastroenteritis and is one of the leading causes of food-borne bacterial diarrhoea globally.

In 2022, salmonellosis caused 60 000 confirmed human cases and was the most frequent cause of food-borne outbreaks, accounting for 17.6% of all food-borne outbreaks. Non-typhoidal Salmonella is associated with a low mortality rate, but EFSA has estimated that the overall economic cost of human salmonellosis could be as high as EUR 3 billion a year ([161]).

In animals, overall resistance to fluoroquinolones (ciprofloxacin) was observed at very high levels in isolates from broiler (55.5%) and fattening turkey flocks (57.9%), at a high level in isolates from laying hens (24.7%) and at a moderate level in Salmonella isolates from fattening pigs (10.1%) and cattle under 1 year of age (12.7%) from data reported in

([159]) EMA guidance document on the use of medicinal products, 12 July 2024.
([160]) WHO- Weekly epidemiological record 2018.
([161]) https://www.efsa.europa.eu/en/topics/topic/salmonella.

2021. Extremely high resistance rates to ciprofloxacin were also reported in *Salmonella enterica* serovar Kentucky isolates from broilers (84.2%), laying hens (82.1%) and fattening turkeys (100%).

In humans in 2022, the overall resistance to ciprofloxacin was 18.7% in Salmonella isolates. The lowest levels were observed in monophasic *S. enterica* serovar Typhimurium (9.6%). High to extremely high levels were observed in *Salmonella infantis* (40.1%) and *Salmonella enterica* serovar Kentucky (72.7%). Combined resistance to both ciprofloxacin and cefotaxime was very low overall in *Salmonella* spp. (0.9%).

Resistance trends calculated for 2013–2022 for human data showed statistically significant increasing trends in resistance to ciprofloxacin in 9 countries and decreasing trends in 3 countries ([162]). By serovar, statistically significant increasing trends in resistance to ciprofloxacin/quinolones were more commonly observed than decreasing trends in all investigated serovars except for *S. enterica* serovar Kentucky.

The WHO's BPPL categorises the treatability of fluoroquinolone-resistant non-typhoidal Salmonella as high/medium, indicating that there are qualitative antibiotic options available for treatment of infection by this pathogen. Alternative antibiotics (e.g. third-generation cephalosporins or azithromycin) may be used, but rising resistance to these drugs poses additional challenges.

There are currently no authorised vaccines for non-typhoidal Salmonella, but a few are under development. Non-typhoidal Salmonella is included in the third group (Group C) of the WHO's vaccines feasibility classification (i.e. pathogens with vaccine candidates either in early clinical trials or with moderate to high feasibility of vaccine development).

The WHO's 2022 pipeline analysis indicated that one vaccine is currently in Phase 1 – a trivalent conjugate vaccine developed by Bharat Biotech, the Centre for Vaccine Development and the University of Maryland. In the EU, a new vaccine that is based on the highly cost-effective Generalized Modules for Membrane Antigens (GMMA) technology is currently being developed by GSK (iNTS-GMMA vaccine). The vaccine includes outer membrane exosomes released by genetically modified *Salmonella enterica* serovars Typhimurium and Enteritidis, the most common causative agents in sub-Saharan Africa.

5.4. Fungal infections

Antifungal-resistant fungal pathogens (e.g. certain species of genus *Candida*) can lead to healthcare-associated infections, particularly in intensive care units, surgical wards and other healthcare settings. This can contribute to the spread of resistant strains and increase the burden on healthcare systems. Antifungal resistance can also impact agriculture and the environment. Resistant fungal pathogens in crops and soil can affect food security, agricultural productivity and ecosystem health.

([162]) The European Union summary report on antimicrobial resistance in zoonotic and indicator bacteria from humans, animals and food in 2022–2023. Increasing trend in Austria, Germany, Hungary, Lithuania, the Netherlands, Norway, Poland, Romania and Slovakia; decreasing trend in Spain, France and Malta.

Invasive fungal infections are a particularly concerning threat for immunocompromised patients, who represent a growing proportion of the population (**Error! Bookmark not defined.**).

The global burden of antifungal resistance infections remains unclear, but fungal infections are estimated to affect over a billion people and cause more than 1.5 million deaths annually worldwide ([163]).

Resistance to antifungal drugs is an emerging worldwide threat. It includes the emergence of infections caused by fungal pathogens such as azole-resistant *Aspergillus fumigatus* (*A. fumigatus*), azole-resistant *Candida parapsilosis*, azole–echinocandin-resistant *Nakaseomyces glabratus*, as well as transmission of multidrug-resistant and pan-resistant *Candidozyma auris* (formerly *Candida auris)* and terbinafine-resistant *Trichophyton indotineae* ([164]).

Fungi have unfortunately been excluded from most AMR surveillance programmes. *Candida* spp. and azole-resistant *A. fumigatus* are the pathogens that feature the most in national and international surveillance programmes ([165]).

This section will focus on the four most critical fungi based on the FPPL classification: *Candidozyma auris, Candida albicans*, *Aspergillus fumigatus* and *Cryptococcus neoformans*. There are no approved fungal vaccines for these pathogens, but a number of studies have shown promising results in animal models and human studies.

5.4.1. Aspergillus fumigatus

Antifungal resistance in *Aspergillus fumigatus* (a common cause of invasive aspergillosis) is also a growing concern. In particular, azole resistance has been reported in different regions, posing challenges for the treatment of aspergillosis. Echinocandins such as caspofungin and micafungin are effective alternative treatments for patients with infections resistant to azoles.

5.4.2. Cryptococcus neoformans

The burden of infections by *C. neoformans* in EU/EEA remains low, but immunocompromised patients are at risk. The significant resistance observed in some pathogens (e.g. *Candida* and *Aspergillus*) to nearly all clinically approved antifungal agents is not seen among *Cryptococcus* isolates, where fluconazole is the primary concern. Amphotericin B (either alone or in combination with flucytosine) remains the gold-standard treatment for systemic cryptococcal infections, with minimal development of clinically significant resistance ([166]).

5.4.3. Candidozyma auris and *Candida albicans*

Candidozyma auris is emerging as a significant concern due to its resistance to multiple antifungal medications, including the three major antifungal classes: azoles, echinocandins and polyenes ([167]). This multidrug-resistant yeast species has been associated with healthcare-associated outbreaks and is challenging to treat. *C. auris* is typically not a

([163]) Global and Multi-National Prevalence of Fungal Diseases – Estimate Precision – J Fungi 2017.
([164]) The rapid emergence of antifungal-resistant human-pathogenic fungi – PubMed (nih.gov).
([165]) Tackling the emerging threat of antifungal resistance to human health | Nature Reviews Microbiology.
([166]) Antifungal Resistance in Cryptococcal Infections – PMC.
([167]) Eurosurveillance: Increasing number of cases and outbreaks caused by Candida auris in the EU/EEA, 2020 to 2021.

danger to healthy individuals, but it does pose a high risk to severely ill patients, those with invasive medical devices and those with prolonged healthcare stays. Its ability to resist multiple antifungal drugs, easy transmission in healthcare settings and potential to cause severe and often fatal infections make it a critical AMR concern. *C. albicans* remains the leading cause of invasive candidiasis, which can lead to mortality rates higher than 40% despite antifungal intervention, and is showing higher rates of azole resistance (especially in LMICS).

Other *Candida* species (e.g. *Candida glabrata* and *Candida krusei*) have shown increasing resistance to antifungal agents, particularly azoles and echinocandins.

In 2019, the GLASS expanded to include fungal infections through the GLASS-FUNGI module, which specifically focuses on invasive Candida bloodstream infections.

In September 2025, the ECDC conducted its latest survey to assess the epidemiological situation, laboratory capacity and preparedness for the emerging fungal pathogen *C. auris* within the EU/EEA. The results confirmed that *C. auris* continues to spread quickly across European hospitals, posing a serious threat to healthcare patients and healthcare systems. Between 2013 and 2023, EU/EEA countries reported over 4 000 cases, with a significant jump to 1 346 cases reported by 18 countries in 2023 alone. 5 countries (Germany, Spain, Greece, Italy and Romania) accounted for most of the cases over the decade. The number of *C. auris* infections is clearly rising, but the true scale of the problem is likely to be under-reported in the absence of systematic surveillance and mandatory reporting. The findings highlight the importance of early detection and control of transmission to avoid widespread rapid dissemination ([168]).

The Council Recommendation on stepping up EU actions against AMR ([169]) encourages the EU Member States to designate an infection caused by *C. auris* that is resistant to last-line treatment as a notifiable disease. The development and deployment of diagnostic tools as well as effective diagnostic capacity for screening and surveillance of *Candida* spp. and other infections with antimicrobial-resistant fungi is therefore crucial for early detection, targeted treatment and preventing the spread of resistance.

6. THREATS RELATED TO LACK OF ACCESS TO ANTIBIOTICS

Ensuring timely access to new and existing antibiotics is critical in the combat against AMR because limited access to effective antibiotics poses a risk to patients and drives the development of resistance.

Access to new antibiotics is often delayed or limited because they are only launched in larger markets. Access to many existing antibiotics is undermined by supply-chain problems or by their withdrawal due to low profitability.

([168]) Survey on the epidemiological situation, laboratory capacity and preparedness for Candidozyma (Candida) auris, 2024.

([169]) 2023 Council Recommendation on stepping up EU actions to combat antimicrobial resistance in a One Health approach.

6.1. Temporary unavailability of antibiotics due to shortages

An assessment of the potential impact of antibiotic shortages on patient health and the AMR situation was carried out under the feasibility study on AMR stockpiling commissioned by HERA ([170]), but only limited evidence was available.

Patients might come to harm from antibiotic shortages in one of two ways: either (1) directly because of the unavailability (or a delay in the availability) of an effective therapeutic option for an active bacterial infection; or (2) indirectly through the increased use of second and third-line antibiotics when there is a shortage of first-line antibiotics (this might facilitate the development and spread of resistance against second and third-line antibiotics and aggravate the AMR situation in the long term).

Product-level shortages of antibiotics due to supply-chain disruptions often occur in individual EU Member States, but EU-wide shortages are rare. The central EMA database ([171]) lists two EU-wide shortages for antibiotics between 2013 and August 2022. Both were for 'reserve' antibiotics: ceftazidime/avibactam and tigecycline. A third relevant EU-wide shortage concerned piperacillin/tazobactam, which is a potential first-line choice in many EU Member States for the treatment of specific types of healthcare-associated infections (including pneumonia).

Product-level shortages do not necessarily lead to patient harm – provided that effective and safe treatment alternatives remain available to patients in a timely manner. Those alternatives can be (1) other products with the same active antibiotic substance ('ampicillin brand B' instead of 'ampicillin brand A'); (2) other antibiotic substances from the same class with a highly similar clinical profile (amoxicillin per oral (p.o) route instead of ampicillin p.o. route); or (3) antibiotics from other classes with similar efficacy.

However, these substitution options could be inadequate in specific clinical contexts and in a few instances (e.g. infections caused by carbapenemase-producing *K. pneumoniae*). For example, ceftazidime/avibactam was, at the time, the first and only licensed βlactam/βlactamase inhibitor effective against such pathogens and alternatives like colistin were generally less effective and more toxic. There is nevertheless some limited evidence that both EU-wide antibiotic shortages listed by EMA in the last 10 years might have caused direct harm to patients. --

This analysis cannot rule out the possibility that shortages might have harmed individual patients – due, for example, to delays in the onset of therapy or to the delay and side-effects caused by cross-class substitution of antibiotics. Furthermore, this analysis does not include the financial impact on patients in cases where payers refuse to pay higher prices for imported substitutes. However, the authors state that these data indicate that the overall likelihood of patients being directly and negatively affected by the absolute unavailability of effective treatments was limited over the entire reported time frame (both for EU-wide antibiotic shortages and for those in the countries assessed). The study concludes that antibiotic shortages are unlikely to be a dominant driver of AMR in the EU.

([170]) HERA AMR feasibility study on stockpiling, final report, 30 September 2022.
([171]) Public information on medicine shortages | European Medicines Agency (europa.eu).

6.2. Delay or lack of commercial launch for novel antibiotics

A study published in 2021 ([172]) analysed the commercial availability in the Group of Seven (G7) plus 7 high-income countries in Europe of the 18 antibacterial agents approved in Canada, the EU, Japan and the US during the decade between 1 January 2010 and 31 December 2019. The results showed in numbers the days from the authorisation granted to the market launch of the product. The study drew the following general conclusions (see Table 2 below, which was extracted from the study).

- Most agents were accessible in only 3 countries (Sweden, the UK and the US). The other 11 high-income countries had access to fewer than half of the agents.
- Centralised marketing authorisation did not lead to automatic European access because, although 14 of the agents were authorised by the Commission, far fewer were commercially launched in practice. It is important to note that centralised marketing authorisation allows the product to be marketed in any or all countries In the EU/EEA where a company decides to commercialise it. This flexibility means that companies can choose to launch their product in some or all EU/EEA countries based on their business strategy, market demand, regulatory considerations and other factors.
- Canada and Japan had the fewest commercial launches, with just 2 and 5 of the total 18 respectively.

INN	First Approval	US	EMA	UK	Sweden	France	Germany	Italy	Norway	Spain	Greece	Romania	Croatia	Denmark	Japan	Canada	Launches
Cefiderocol	14 Nov 2019	102	23 Apr 2020 (161)	Yes (306)	Yes (413)	No	No	No	No	No	No	No	No	No	No	No	3
Lascufloxacin	20 Sep 2019	No	No	No	No	No	No	No	No	No	No	No	No	No	Yes (103)	No	1
Lefamulin	19 Aug 2019	21	27 Jul 2020 (343)	No	No	No	No	No	No	No	No	No	No	No	No	No	1
Imipenem-cilastatin/ relebactam	16 Jul 2019	321	13 Feb 2020 (212)	Yes (382)	Yes (382)	No	No	No	Yes (290)	No	No	No	No	No	No	No	4
Omadacycline	2 Oct 2018	122	No	No	No	No	No	No	No	No	No	No	No	No	No	No	1
Sarecycline	1 Oct 2018	92	No	No	No	No	No	No	No	No	No	No	No	No	No	No	1
Eravacycline	27 Aug 2018	35	20 Sep 2018 (24)	No	No	No	No	No	No	No	No	No	No	No	No	No	1
Plazomicin	25 Jun 2018	6	No	No	No	No	No	No	No	No	No	No	No	No	No	No	1
Meropenem/ vaborbactam	29 Aug 2017	33	20 Nov 2018 (448)	Yes (815)	Yes (1037)	Yes (1064)	No	No	No	No	No	No	No	No	No	No	4
Delafloxacin	19 Jun 2017	196	16 Dec 2019 (910)	Yes (1121)	No	No	No	No	No	No	No	No	No	No	No	No	2
Bezlotoxumab	21 Oct 2016	115	18 Jan 2017 (89)	Yes (174)	Yes (131)	Yes (1045)	Yes (527)	Yes (618)	Yes (206)	Yes (557)	No	No	No	No	Yes (413)	No	9
Ceftazidime/ avibactam	25 Feb 2015	35	23 Jun 2016 (484)	Yes (748)	Yes (827)	Yes (1967)	Yes (720)	Yes (1049)	Yes (310)	Yes (999)	Yes (980)	Yes (933)	Yes (1184)	Yes (841)	No	No	12
Ceftolozane/ tazobactam	14 Dec 2014	49	18 Sep 2015 (278)	Yes (352)	Yes (383)	Yes (598)	Yes (322)	Yes (657)	Yes (383)	Yes (443)	Yes (383)	Yes (808)	Yes (657)	Yes (352)	Yes (1630)	Yes (291)	14
Oritavancin	6 Aug 2014	56	18 Mar 2015 (224)	No	No	No	No	No	No	No	No	No	No	No	No	No	1
Tedizolid	20 Jun 2014	10	23 Mar 2015 (276)	Yes (315)	Yes (438)	Yes (577)	Yes (276)	Yes (1046)	Yes (390)	Yes (294)	Yes (681)	Yes (742)	No	Yes (276)	Yes (1432)	No	12
Dalbavancin	23 May 2014	39	19 Feb 2015 (272)	Yes (914)	Yes (1279)	Yes (1097)	Yes (918)	Yes (740)	No	Yes (619)	Yes (954)	Yes (862)	Yes (923)	No	No	No	10
Fidaxomicin	27 May 2011	35	5 Dec 2011 (192)	Yes (371)	Yes (371)	Yes (542)	Yes (585)	Yes (889)	Yes (385)	Yes (554)	Yes (432)	Yes (797)	Yes (1711)	Yes (371)	Yes (2651)	Yes (1648)	14
Ceftaroline	29 Oct 2010	64	22 Aug 2012 (663)	Yes (726)	Yes (764)	Yes (844)	Yes (717)	Yes (1007)	Yes (755)	Yes (1162)	Yes (1315)	Yes (795)	Yes (2764)	Yes (734)	No	No	12
No. approved or launched	18	17	14	11	10	8	7	7	7	7	6	6	5	5	5	2	

*Table 2: Analysis of the commercial availability in the Group of Seven (G7) plus 7 high-income countries in Europe (*Canada, Croatia, Denmark, France, Germany, Greece, Italy, Japan, Norway, Romania, Spain, Sweden, United Kingdom, and United States.). *Approval and commercial launch in 14 high-income countries of new molecular entity antibacterials first approved by the United States Food and Drug Administration (FDA), the European Medicines Agency (EMA), the Japanese Pharmaceuticals and Medical Devices Agency, or Health Canada, 2010-2019. 'No' indicates 'not commercially launched', except in the EMA column where 'No' indicates 'not approved by EMA'. Numbers indicate the lag from first approval to commercial launch in days, except in the EMA column where numbers indicate the lag from first approval to EMA approval in days. The US was the country for all first approvals and first commercial launches, except for lascufloxacin, which was approved and launched only in Japan. Abbreviations: EMA, European Medicines Agency; INN, International Nonproprietary Name; UK, United Kingdom; US, United States. Source: Outterson et al. ([172]).*

In 2024, HERA conducted a survey of the EU/EEA countries in preparation for a pilot multi-country revenue- guarantee initiative to improve availability and access to new or recently authorised antibiotics. 24 countries expressed an interest in participating in the

([172]) Patient Access in 14 High-Income Countries to New Antibacterials Approved by the US Food and Drug Administration, European Medicines Agency, Japanese Pharmaceuticals and Medical Devices Agency, or Health Canada, 2010–2020 | Clinical Infectious Diseases | Oxford Academic (oup.com).

pilot, thus confirming inadequate access to newly approved antibiotics in the EU/EEA (unpublished data).

7. CONCLUDING REMARKS

The rise of AMR remains a significant threat to health in the EU and globally. Since the last threat prioritisation report in 2022 (not published), the WHO has updated the list of **bacterial priority pathogens** in which pathogens from the Enterobacterales order that are resistant to third-generation cephalosporins are now considered critical. In parallel, 2024 ECDC surveillance data continued to show increasing trends in AMR percentages such as those caused by carbapenem-resistant Enterobacterales and vancomycin-resistant *E. faecium.* In February 2025, the ECDC issued a rapid risk assessment that highlighted an increase of carbapenem resistance in Enterobacterales, such as *K. pneumonia and E. coli*, in the EU/EEA. Further analysis is needed in order to assess how much the priorities established at the global and European levels differ regionally and between EU Member States (for example, as of 2022, 9 EU countries had reported a resistance rate of *Acinetobacter* spp. to carbapenems of less than 5% while 11 EU Member States had reported resistance rates exceeding 50% ([173])).

The long-term consequences of the COVID-19 pandemic on antibiotic consumption and on estimated AMR incidence are still difficult to fully understand and vary depending on the context and drug-pathogen combinations considered. However, the Ukraine war and other forced displacements are an aggravating factor for the emergence and spread of resistance.

The 2024 WHO list of bacterial priority pathogens includes rifampicin-resistant *Mycobacterium tuberculosis*. This serves as a reminder that **MDR and XDR-TB** remain a critical challenge that needs to be addressed, especially in high-burden regions.

The increasing rates of AMR in *N. gonorrhoeae* (particularly the emergence of **extensively drug-resistant *N. gonorrhoeae***) remains a major global public health concern. This underscores the need to invest in the development of new and effective treatments against these priority pathogens.

Fungal priority pathogens (including *Cryptococcus neoformans, Candidozyma auris, Aspergillus fumigatus* and *Candida albicans*) need greater attention because they pose a growing threat due to their multidrug resistance – particularly to immunocompromised patients.

The results of the AMR surveillance coupled with an analysis of the AMR pipeline are making it easier to identify the most threatening pathogens.

The **antibiotics** pipeline analysis shows that, while the number of antibacterial agents in clinical development increased in 2023, it is still not sufficient to address serious infections and to complement antibiotics that are becoming ineffective due to AMR. The current pipeline continues to show a **major gap in antibacterials** that are **effective against metallo-β-lactamase (MBL) producers,** while the **prevalence of those enzymes in resistant pathogens is increasing. Alternatives to antibiotics** such as the use of

([173]) Surveillance Atlas of Infectious Diseases (europa.eu) 2022 data.

bacteriophages and **monoclonal antibodies** may become available and serve as **alternative treatment options** in the near future**.**

Advances in **diagnostics** are vital for addressing the challenges of AMR and will ensure that new antibacterial agents are used effectively. The 2023 WHO antibacterial pipeline highlights a shift towards the development of narrow-spectrum antibacterials. This will probably require **greater use of rapid diagnostics to ensure that these narrow-spectrum products are used in the correct patients**. The WHO is currently developing an analysis of the pipeline for both fungal and bacterial diagnostics. The results from this pipeline analysis will inform HERA's support for the development of diagnostics in the AMR field.

Both **vaccines** against viral and bacterial infections can contribute to reduce the spread of infections and AMR by preventing the need for a treatment with antimicrobials. By lowering infection rates, vaccines not only protect individuals but also reduce the overall circulation of pathogens in the community, limiting opportunities for resistant strains to emerge and spread. New vaccines are under development, but **vaccines against high-priority bacterial pathogens are still lacking and will require time to be developed**.

In addition to the insufficient level of innovation, the **lack of availability of certain antibiotics in the EU has the potential to worsen the AMR threat** – either by causing a direct risk for the patients or by hindering the proper use of antibiotics and consequently promoting AMR emergence and spread.

In conclusion, the AMR threat includes a variety of drug-pathogens combinations that cause different conditions and have different drivers. A wide arsenal of MCM against this multifaceted and complex threat is needed, but this is currently compromised by lack of innovation and lack of access. Commission's strategy to address this priority is therefore a multifaceted approach that includes a combination of push and pull interventions to ensure the development of new antibacterials as well as the availability and access of both new and existing antibacterials.

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