The global need for hyperimmune IgG (HIG)

(Often neglected essential medicines)

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Today's key points

A	B	C	D
• What HIG are	• Why they are time-critical	• Why shortages occur	• What can be done

Hyperimmune IgG (HIG)

- Plasma-derived IgG with **high titers** of antibodies against a **single defined target** (e.g., rabies virus, HBV, tetanus toxin, RhD).

How HIG differs from IVIG in clinical use

IVIG

- used chronically across a wide range of indications, including primary and secondary immunodeficiencies and autoimmune disorders

HIG

- Life-saving when administered within hours after exposure to specific pathogens, antigens, or toxins.
- Typically administered once or a few times, at a moment when any delay can irreversibly change the clinical outcome

Essential for pre-exposure (PrEP) and post-exposure (PEP) prophylaxis

Anti-D is the “flagship”,

but HIG represent a broader and fragile PDMP family

- **HIG = a group of low-volume PDMPs characterized by:**
  - **time-critical use**
  - **Major clinical impact when unavailable**

Exposed to “last-mile” failures (do not reach the patient on time)

HIG

Included in major essential/critical medicine lists

These are time-critical medicines: delays can cost lives

Global

WHO EML listing

Anti-D Ig; Anti-rabies Ig; Anti-tetanus Ig

Regional

EMA list of Critical Medicines

Anti-D Ig; Anti-rabies Ig; Anti-tetanus Ig

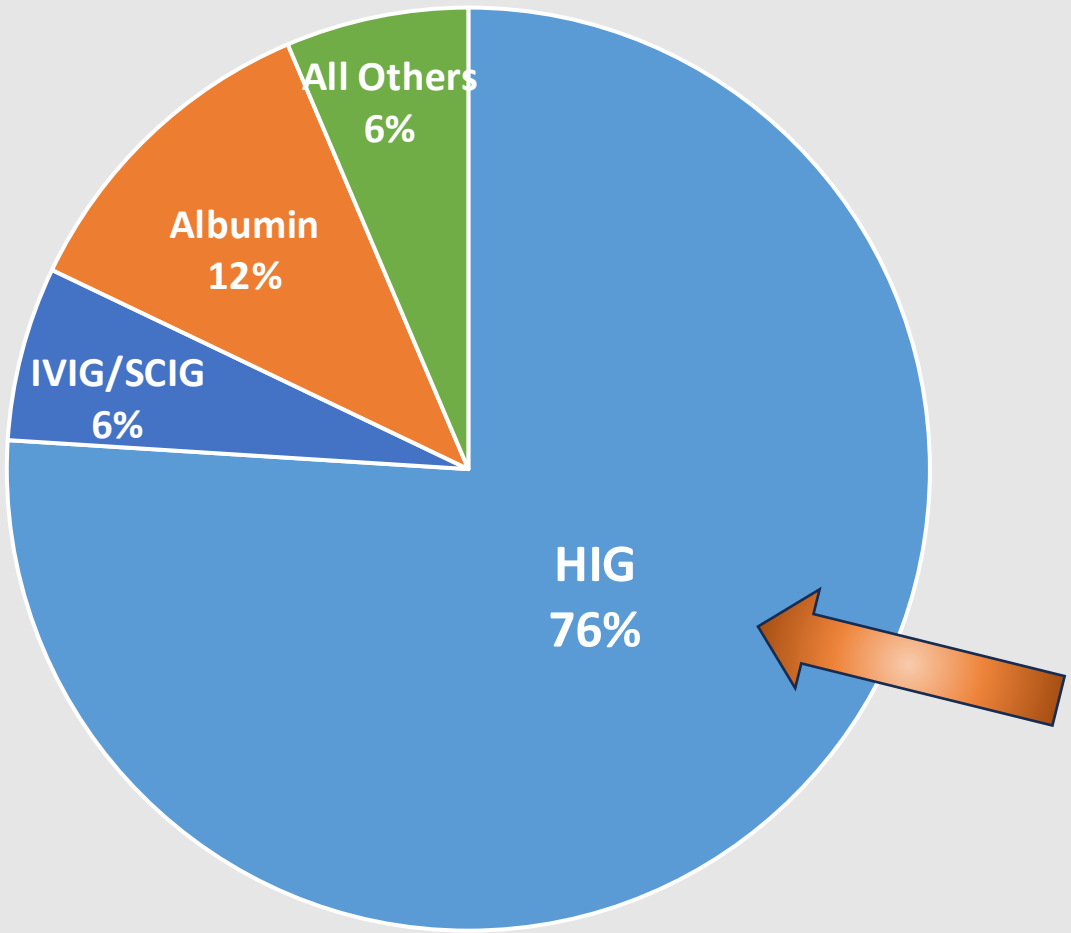
National example (France): ANSM monitoring of shortages of critical medicine, including HIG

Additional HIG in EML of LMICs

Anti-hep B Ig; Anti-varicella-zoster Ig

Patient Population by PDMP received worldwide (2022)

% people administered a PDMP by Product



≃ 16.5 million people received a PDMP worldwide:

- 12.5 million: HIG
- 1.0 million: IVIG
- 1.9 million: albumin
- 1.0 million: another PDMP
- 100,000: coagulation factors and others

76 % !

Source of HIG plasma and HIG: some facts

Most from USA and Asia (immunized donors)

Most E.U countries prohibit or restrict donor immunization

--- > 100% dependent on the U.S. for HIG supply.

Europe produces very little anti-tetanus Ig

No EU country produces anti-rabies plasma

Latin America and the Middle-East have no HIG plasma, all their products are imported

Contract plasma fractionation of HIG is uncommon

Most of the HIG supply is of commercial origin

Generally just 1-3 suppliers or distributors in a particular country

Reflects a very fragile situation of dependency

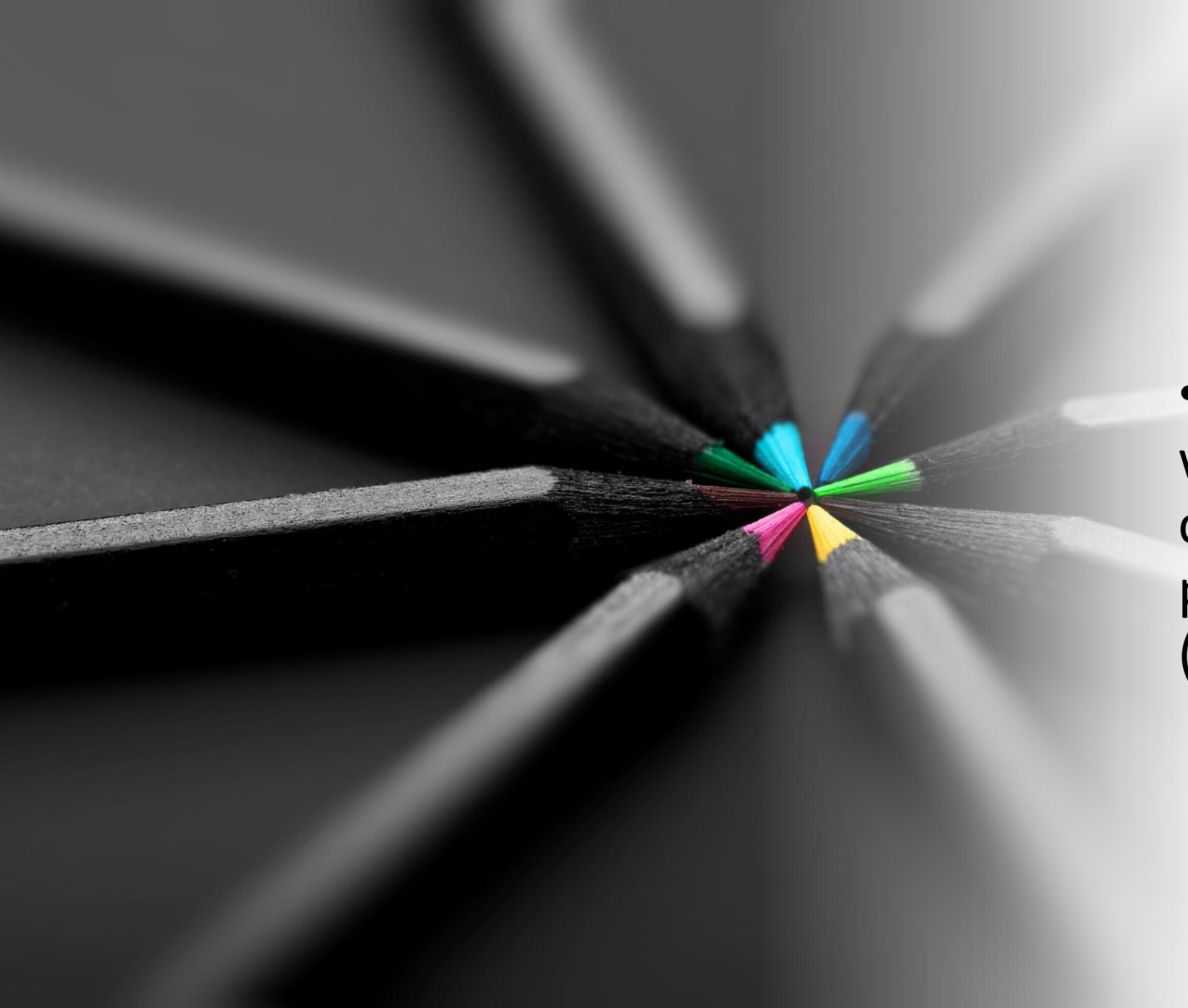
Why lack of HIG is a serious medical concern

Efficacy based on PEP and PrEP principles

Provide “fast protection” during the window prior to vaccine-induced immunity

Effectiveness depends not only on biological activity, but also on timely availability.

Delayed access or lack of product compromise the efficacy of the PEP strategy, even if vaccines and clinical guidelines are applied.



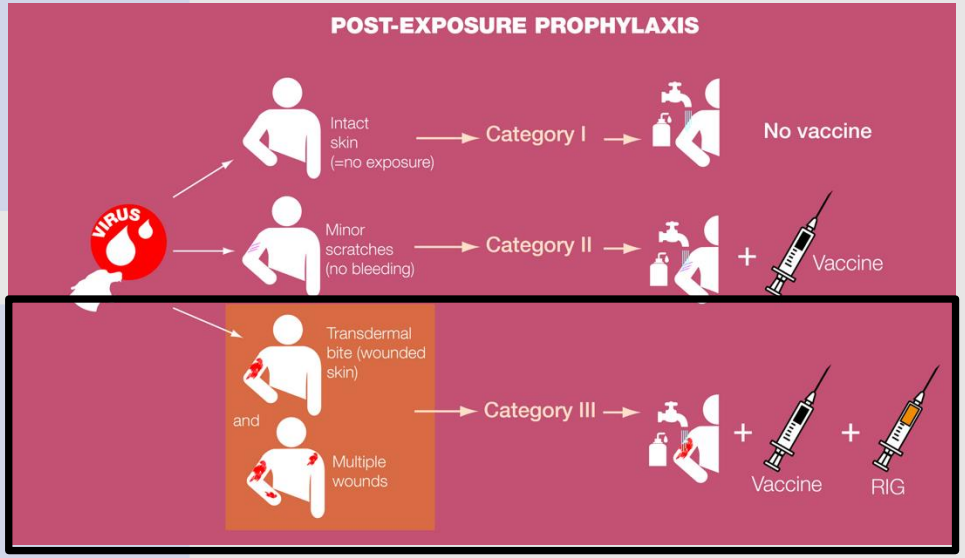
- A few examples of why lack of HIG is a critical medical problem globally (LMICs and HICs)

Anti-rabies (HRIG)

Critical example where time-critical prophylaxis is vital

Rabies

- 59’000 deaths/year, affecting > 150 countries, mainly in Africa and Asia
- Vaccines and HRIG are often inaccessible/unaffordable



WHO PEP includes

- wound care + vaccine
- + HRIG for **category III** exposures in immunologically naïve people.

=== > missing HRIG product

can mean death

- Tens of millions of people require medical assessment for possible exposure each year
- Of concerns to HIC populations (travel, contacts with wildlife, imported cases)

(https://www.who.int/news-room/fact-sheets/detail/rabies)

Anti-tetanus toxin (HTIG)

Rapid post-exposure passive HTIG immunotherapy can prevent severe disease

Tetanus

- Maternal and neonatal tetanus: major public-health issue with very high case-fatality in neonates
- In 2018, about 25 000 newborns died from neonatal tetanus,

https://www.who.int/news-room/fact-sheets/detail/tetanus

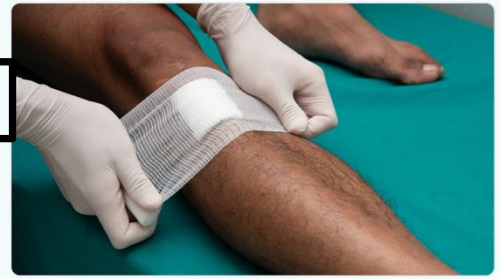
Passive antitoxin therapy

- Prophylaxis after tetanus-prone wounds in people not fully protected by vaccination
- Treatment of suspected/confirmed tetanus, together with wound debridement, antibiotics, and supportive care.

=== > missing HTIG product can mean death

KEY POINTS

- The best ways to prevent tetanus are vaccination and wound management.
- Tetanus vaccination and TIG prophylaxis may be indicated depending on the wound type and patient's vaccination history.
- Antibiotics (topical or systemic) aren't recommended during wound care to protect against tetanus.
- Follow CDC's immunization schedule to ensure your patients are protected from tetanus.



https://www.cdc.gov/tetanus/hcp/clinical-guidance/index.html

Anti-Hepatitis B (HBIG)

Prevention of mother-to-child transmission

is a vital control strategy

Hepatitis B

- 54 million people living with chronic hepatitis B infection
- 1.2 million new infections each year.
- 1.1 million deaths (cirrhosis and hepatocellular carcinoma (primary liver cancer).

https://www.who.int/news-room/fact-sheets/detail/hepatitis-b

Passive HBIG therapy

- For infants born to HBsAg-positive mothers: **HB vaccine + HBIG within 12 hours** at different injection sites
- Occupational/community exposures

=== > missing HBIG administration

can mean HBV infection

KEY POINTS

- Hepatitis B virus (HBV) infection in a pregnant patient poses a serious risk to an infant at birth.
- HBV infection in infants can lead to long-term serious health effects if left untreated.
- Perinatal transmission of HBV infection is preventable.
- Vaccination is the best way to prevent HBV infection.

https://www.cdc.gov/hepatitis-b/hcp/perinatal-provider-overview/index.html

Equine plasma derived HIG

F(ab)'2

Rabies, tetanus, botulism, diphtheria…

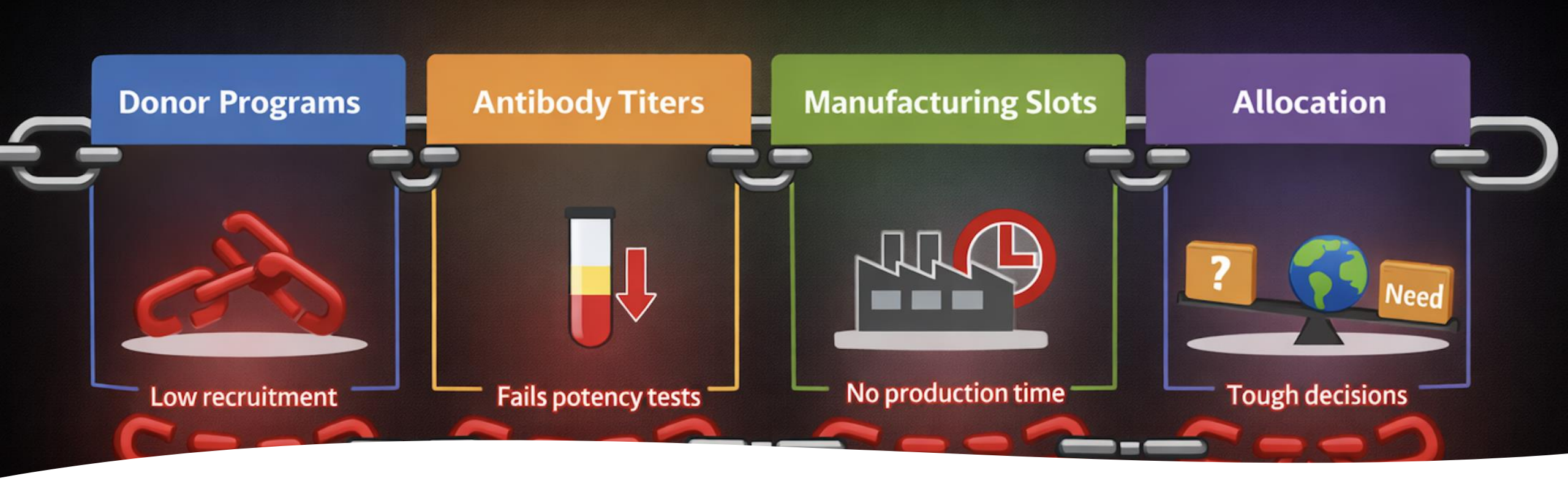
mAb

Rabies, Tetanus (clinical trials)
RhD (?)

Despite alternative products, human plasma-derived HIG remain needed

What sets HIG products apart

Complex donor recruitment and stimulation	Possibly smaller pool products than polyvalent plasmas	The manufacturing know-how existed in EU… but has been lost	Competition with IVIG to industrial fractionation capacity
Rarely included in a contract plasma fractionation program	Variability in titers (donors and manufacturing plasma pools)	Complex inventory and supply channels	No patients' organization (episodic, not stable patients' community)



HIG Production chain: Challenges to address in EU

- **Donor program:** recruiting/re-recruiting *the right donors* (e.g. vaccinated/boosted)
- **Titers / potency:** making sure sufficient titer for the starting plasma pool and HIG product meet titer specifications
- **Manufacturing slots:** needing dedicated fractionation campaigns, segregation, competition to capacity with IVIG and other PDMPs
- **Allocation:** who gets it during shortages; national stock vs routine supply

HIG fractionation technologies

The traditional plasma fractionation processes do not prioritize IgG recovery and have to cope with multiple products

HIG are good candidates for dedicated fractionation processes aiming at high IgG recovery (IgG first!)

Examples of the role of the public and private sectors for guaranteed supply of HIG

Blood establishments: Recruite HIG donors and integrate HIG plasma collection with routine plasma collection (without disrupting routine blood/plasma collections)

Plasma fractionators: Provide "protected manufacturing slots", "dedicated campaigns" for HIG

Policy makers: Facilitate "strategic independence" and preparedness to ensure sufficient supply of high-impact HIGs

National health authorities: Optimize regulations to harmonize donor immunization and selection for HIG plasma, and quality, safety, and potency requirements for finished HIG products

Take-home messages

HIG are critical, time-critical medicines

Their supply chain is fragile and structurally vulnerable

Anticipation, prioritisation, and protected capacity are required

The global need for hyperimmune IgG

(the often neglected essential medicines)

Thank you

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