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Mpox vaccine research

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Lessons-learned workshop on Clinical Trials in Public Health Emergencies

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Innovative clinical research network in vaccinology

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French recommendations

Date	Indication
20/05/2022	Post-exposure vaccination (PEP) of adult contacts at risk as defined by Santé Publique France
07/07/2022	Pre-exposure (PrEP) vaccination of adults at very high risk of exposure : - MSM and trans people with multiple sexual partners - Sexual workers - Professionals in sexual consumption venues
06/10/2022	- Women who are occasional partners or who share the same living space as people at very high risk of exposure (see HAS opinion of 07/07/2022)

What level of evidence on vaccine?

Post-exposure

- Timing : Historical study on smallpox, use of delphi (Massousi, 2003, JID)
- Animal Challenge
- Limited use of Imvanex® in the UK (Adler, LID, 2019) : 7 cases total, 148/162 vaccinated, 2 secondary cases

Pre-exposure

- Historical data on ACAM-2000
- No data on efficacy of Imvanex® on MPXV
- Evidences from immunogenicity studies and virological characteristics.


Good Charlotte
13

First data

- Post-exposure
- Failure rate : 4%
- Likely « optimistic »
  - Lost to follow-up
  - Symptomatic but not sampled
  - Mild diagnosis

➔No control group = No vaccine effectiveness

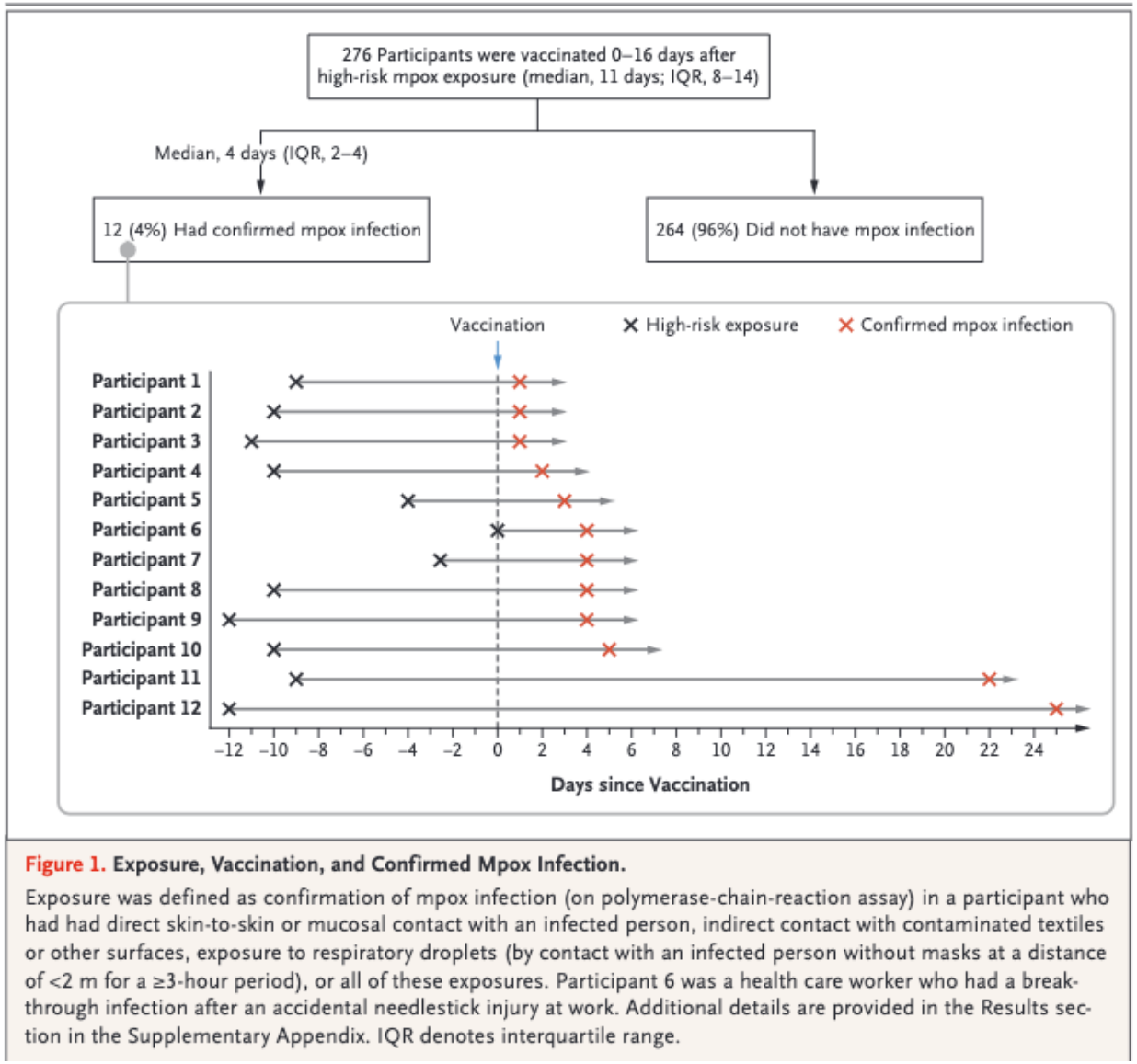


Figure 1. Exposure, Vaccination, and Confirmed Mpox Infection.

Exposure was defined as confirmation of mpox infection (on polymerase-chain-reaction assay) in a participant who had had direct skin-to-skin or mucosal contact with an infected person, indirect contact with contaminated textiles or other surfaces, exposure to respiratory droplets (by contact with an infected person without masks at a distance of <2 m for a ≥3-hour period), or all of these exposures. Participant 6 was a health care worker who had a breakthrough infection after an accidental needlestick injury at work. Additional details are provided in the Results section in the Supplementary Appendix. IQR denotes interquartile range.

Thy et al., 2022, NEJM

How to measure prospectively mpox vaccine effectiveness?

- What efficacy ?
  - Clinical : need a **control** group and a **large** sample size
  - Immunogenicity : no correlate of protection
- What study design ?
  - Interventionnal (randomization) ➔ Ethical and practical issues
  - Observationnal
    - High risk of bias without randomization (behavior change)
    - High risk cohort study ➔ few eligible that are not vaccinated
    - Time series ➔ Doxyvac study
    - Surveillance Database ➔ hardly available
- Time constrain !

Monkey Vax :

- **Main objective:** To estimate the rate of PEV or Pre-EV failure after 1 dose with MVA vaccine in subjects at risk of mpox infection.

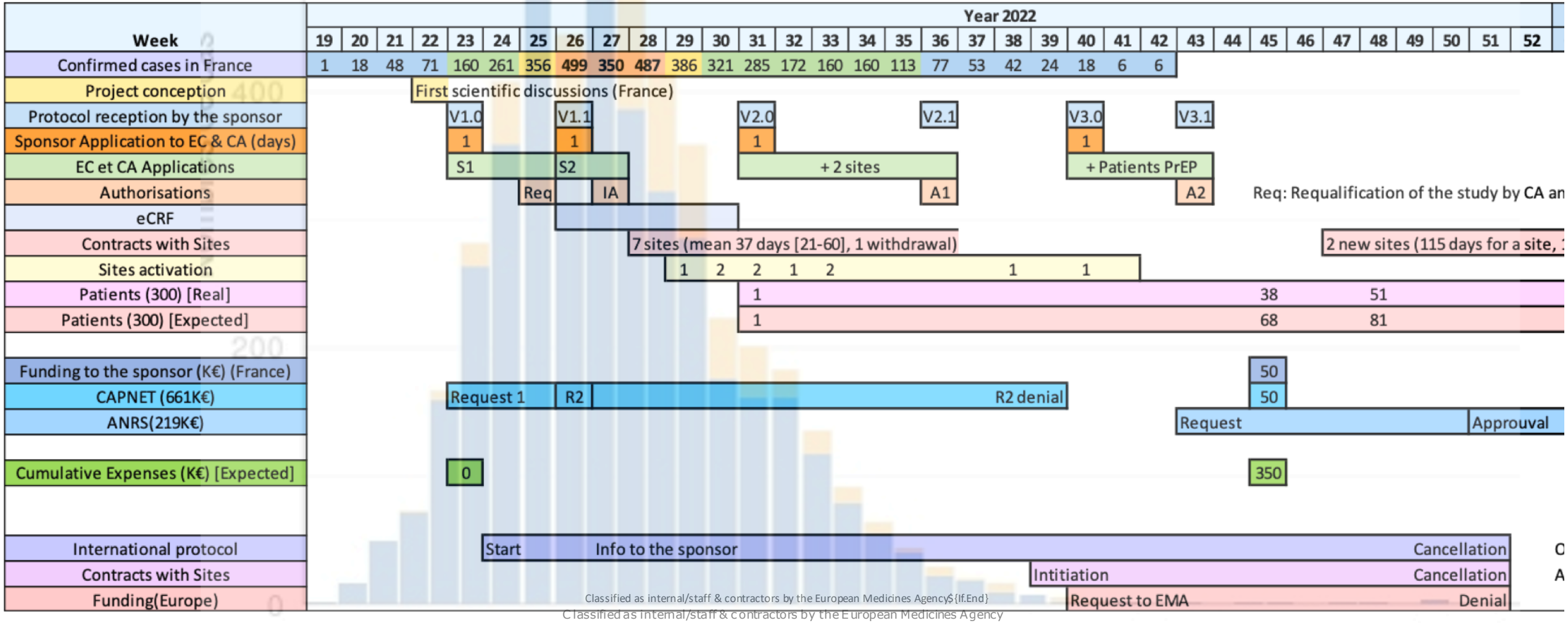
- **Design:** Prospective Cohort Study

- **Regulatory Classification (France):** Submitted as a low risk interventional study, but reclassified by CA as an interventional study with drug administration (but not as IMP)

- **Number of patients:** 100 PEP + 200 PrEP (initially 226 PEP)

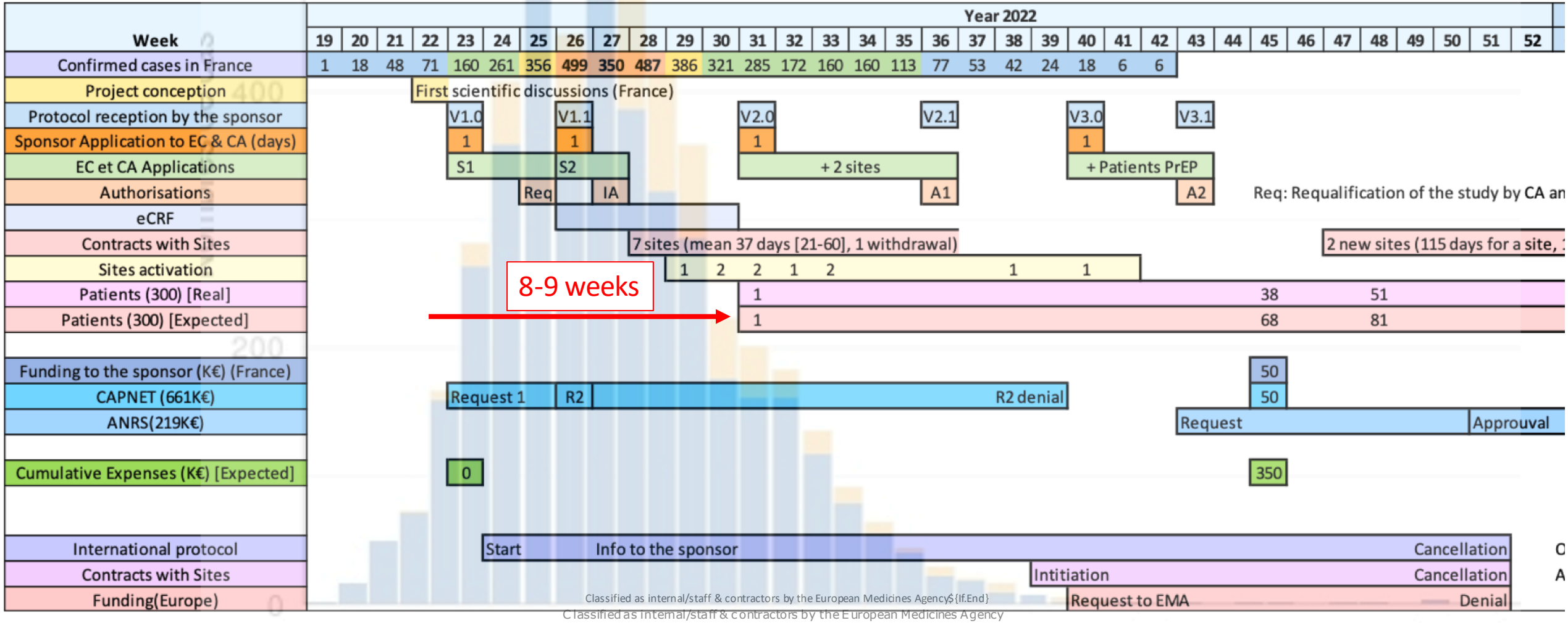
- **Recruitment:** 9 => 15 months // **Follow-up:** 3 => 12 months

Research vs Recommandation vs Epidemic



Classified as internal/staff & contractors by the European Medicines Agency

Research vs Recommandation vs Epidemic



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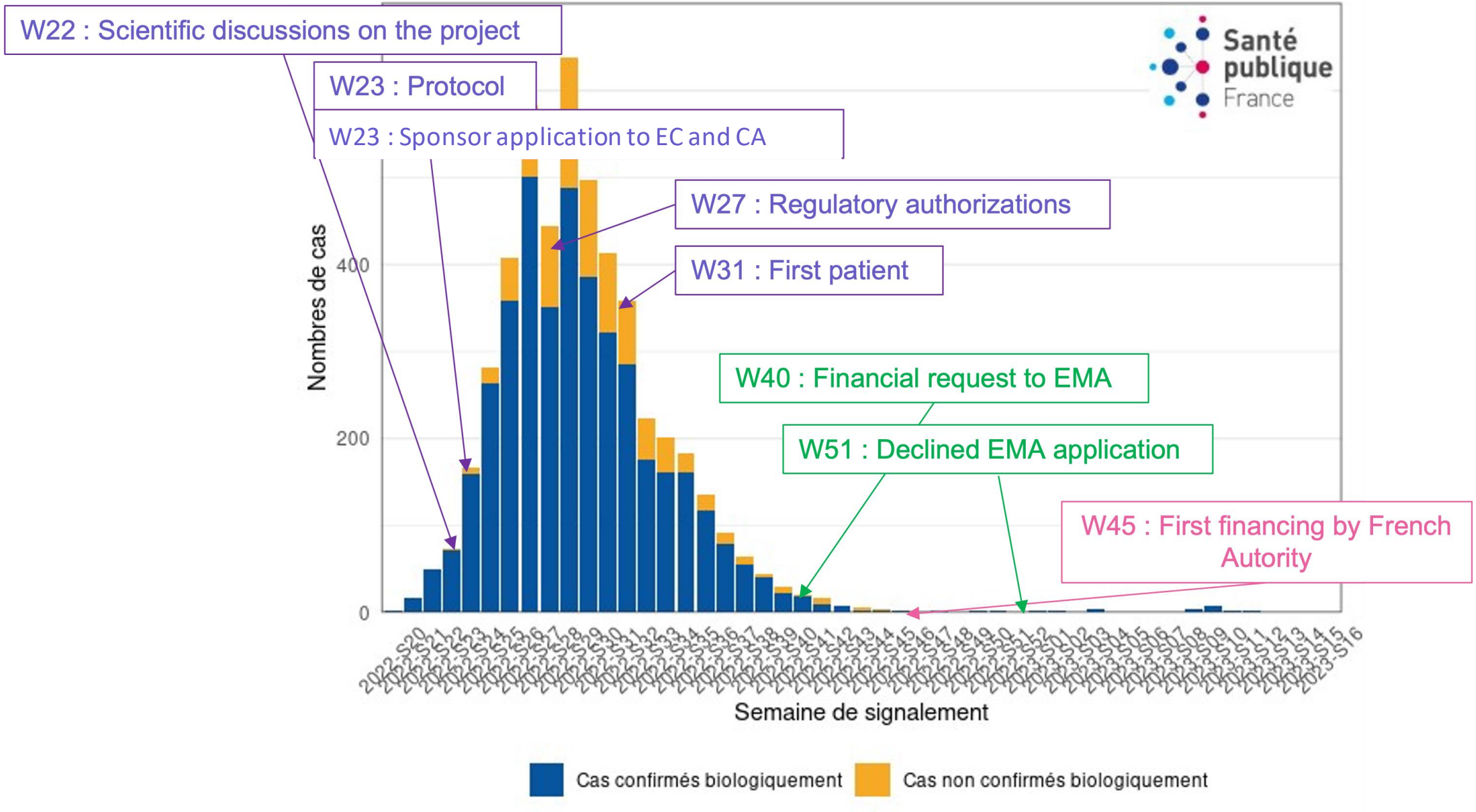

Delays in France…

- **Investigators**
  - From the idea to the protocol = 2 weeks
  - E-CRF activation = 5 weeks
- **Sponsor** = 1 day
- **Regulatory authorities**
  - Application to Authorizations = 5 weeks
  - Amendments Authorizations = 5 weeks
- **Sites**
  - Authorizations to first patient = 5 weeks
  - Sites responsiveness = up to 13 weeks
  - Contracting with sites = 3 to 16 weeks (GDPR + €)
- **Funding**
  - DGOS: 3w to accept and 23w to finance
  - ANRS : 9w to accept and 16w to finance
  - EMA: 12w to refuse

… and barriers in Europe

- Aim : increase the sample size, in a context of limited vaccine doses, possibility of having control group
- Extensive discussions with colleagues from Belgium, Ireland, Portugual, Sweden → Able to agree on protocol
- Scientific and political willingness < Regulation and funding challenges
  - No clear European agreement on the framework (IMP ? Data Monitoring? Safety?)
  - Cannot find National Sponsor to fulfill regulatory requirements (CRF, Contracting)
  - No Funding because no satisfactory control group

Conclusion

- **Partial benefits** from the SARS-CoV-2 experience: Initial responsiveness from Health Authorities but subsequent slowdown (amendments and samples handling)

- Context of **high uncertainty** : epi curve/social environment/data from other settings/studies

- Research strategies, regulation and funding **are intricated**

- Agreement on research protocol <> regulation, and **is not enough**

How to improve altogether?

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➔ Prepare draft protocol and E-CRF

➔ Fast Track

➔ Pre-identified investigation sites

➔ Responsiveness

How to improve altogether?

➔Need for a structured framework to combine [scientific + regulatory + funding + logistic] challenges

➔ Need to be **aligned**

- Researchers : scientific objectives
- Regulation : what legal/framework
- Stakeholders : what is the priority
- Resources : Human (commitment) and Funding

➔ To be able to work in parallel

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Questions?

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