Moderna COVID-19 vaccines and the risk of myocarditis: review of current data and planned studies

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(presenting for the Moderna COVID-19 Vaccine Team)

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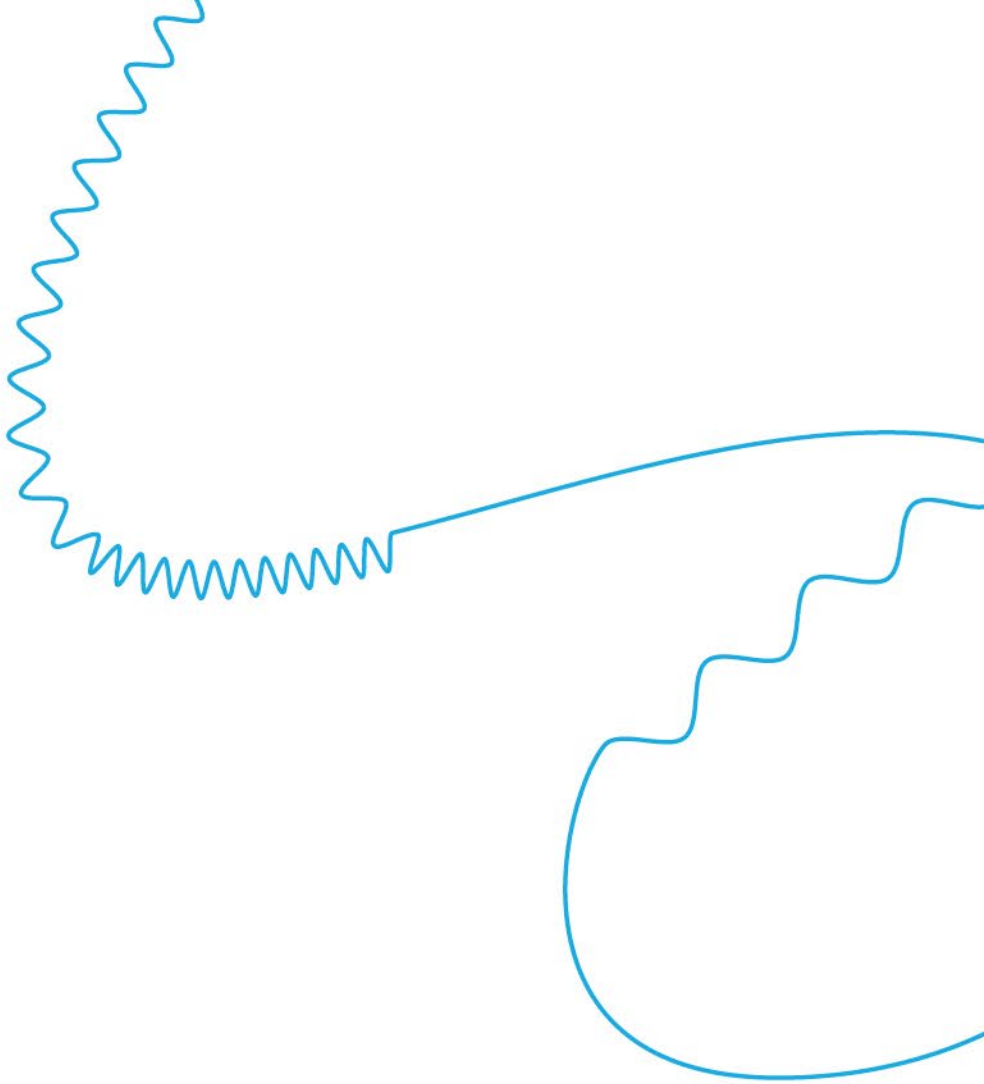

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Moderna has a Comprehensive Set of Activities to Evaluate and Mitigate Risk for Myocarditis and Pericarditis from Clinical Development through Post-authorization/licensure

- US Fact Sheet, SmPC, and CCDS updated as needed
- Informed consent and Investigator's Brochures updated across vaccine platform to advise regarding potential risk for myocarditis and pericarditis
- Clinical trials enhanced for myocarditis / pericarditis detection and evaluation
- Cardiac Event Adjudication Committee
- Observational (real world evidence) studies ongoing with inclusion of booster/ bivalent vaccines
- Ongoing risk evaluation through review of global data, including monthly safety reports

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Post-authorization Safety Assessment

Reporting Rates* of **Myocarditis** within 7 Days per Million Doses of SPIKEVAX Administered, Stratified by Age and Gender – **Doses 1, 2, 3. and 4****
Moderna Global Safety Database (Cumulative to 17 December 2022)

Age Group (years)	Males				Females			
	Dose 1	Dose 2	Dose 3	Dose 4	Dose 1	Dose 2	Dose 3	Dose 4
5 -11	0.00	4.92	0.00	NA	0.00	1.92	0.00	NA
12-17	2.26	24.34	0.59	NA	0.51	2.29	0.27	NA
18-24	4.78	30.05	16.23	0.81	0.93	2.67	1.71	0.00
25-39	2.59	10.68	7.47	0.00	0.85	1.44	1.96	0.27
40-49	0.78	3.44	2.69	0.97	0.51	1.28	1.55	0.00
50-64	0.30	0.90	1.23	0.00	0.39	0.50	0.63	0.00
65-74	0.18	0.47	0.75	0.13	0.13	0.38	0.47	0.10
75+	0.17	0.08	0.41	0.17	0.09	0.19	0.46	0.80

Limited number of reports for myocarditis associated with the bivalent vaccines:

4 cases reported with Bivalent.222 (BA4./BA.5) – 110.7m doses distributed

11 cases reported with Bivalent.214 (Original/BA.1) – 127.4m doses distributed

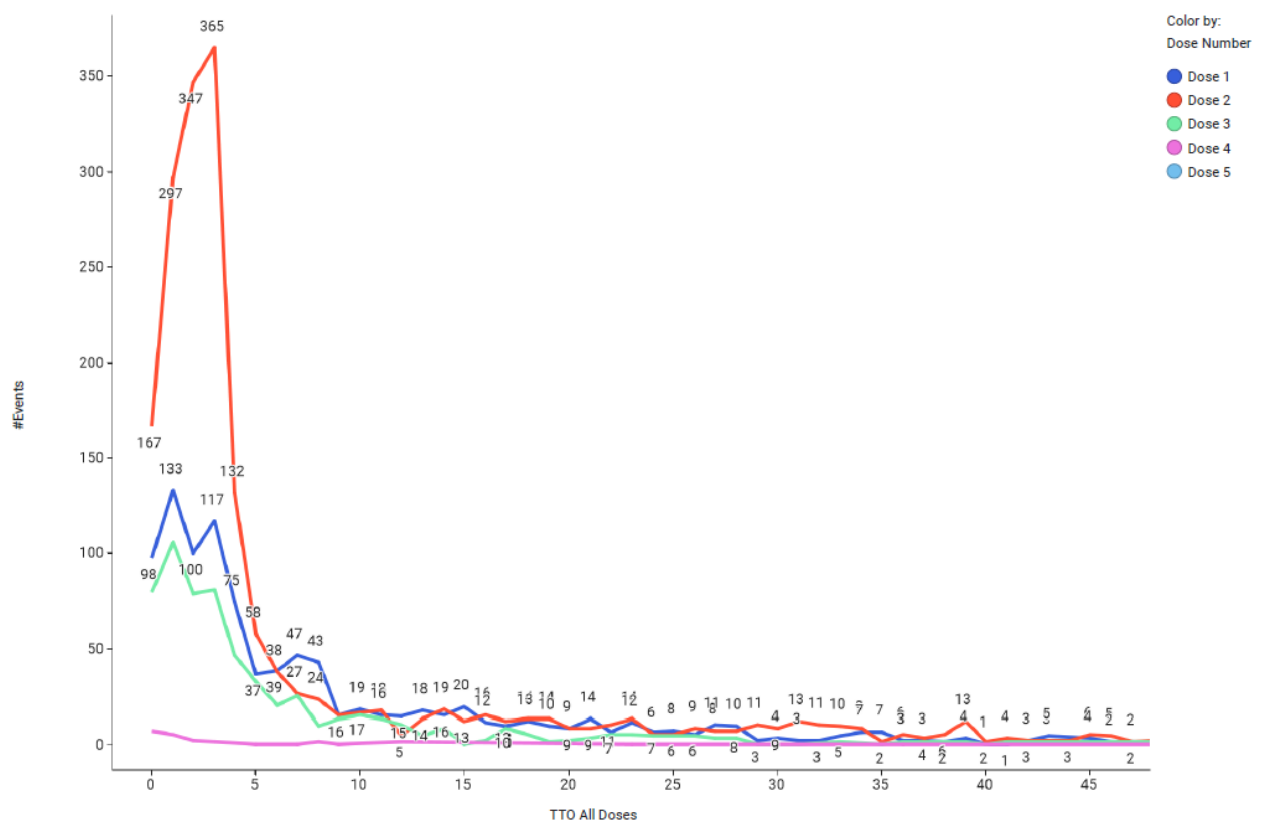
- Based on estimated number of doses administered
- > 408 million 1st doses, >275 million 2nd doses, >166 million 3rd doses, and >62 million 4th doses distributed
- **Third and fourth doses includes both original SPIKEVAX (Original) and SPIKEVAX bivalent booster dose formulations.
- Because of variation in the timing of use of SPIKEVAX bivalent boosters and limited available global data, extrapolation from the US to estimate the use of bivalent boosters was not deemed appropriate.

Cumulative Myocarditis Reports in mRNA-1273 (SPIKEVAX- ORIGINAL) and SPIKEVAX Bivalent Vaccines Recipients (as of Dec 17, 2022) – Moderna Global Safety Database

- 3563 cases reported (3575 events)
  - Males: 2,540 (71.3%)
  - Mean Age: 35.2 years (SD: 16.1 years) (min 7.0/max:94.0)
- 2525 of the cases were medically confirmed*
- Greatest proportion of cases reported in males aged 25-39 years (864; 24.2%) and 18-24 years (774; 21.7%)
- Greatest proportion (1,105; 30.9%) of cases reported after dose 2, with time to onset <7 days (858; 77.6%)
- Of the events with known outcomes, most reported as recovered or recovering (1,687; 47.2%)

*i.e. reported by health care professionals

Distribution of Events by Time to Onset Stratified by Dose Number for SPIKEVAX and SPIKEVAX Bivalent Vaccines – Cumulative to 17 December 2022



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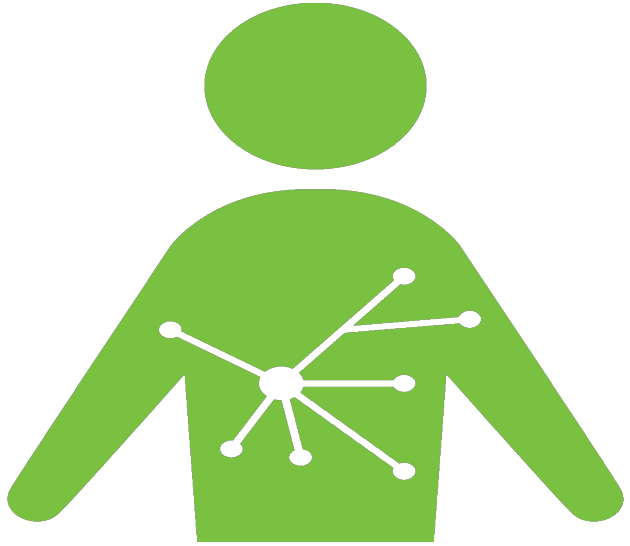

Real World Evidence Program - Myocarditis

Real World Evidence Program for Myocarditis

- Spontaneous reports of any post-authorization/licensure adverse reports are not suitable to determine:
  - Incidence rates and risk estimates
  - Risk factors
  - Natural history
- Robust real world evidence program addresses these topics

Post Authorization Real World Evaluation of Myocarditis

Signal Detection and Refinement

- Using linked healthcare claims:
- Characterize the risk of myocarditis following receipt of Spikevax, and to determine whether the risk varies:
  - By dose, including following booster doses
  - By demographic characteristics including age and sex
  - Within subpopulations of special interest
- Describe the observed cases of myocarditis to examine potential risk factors in general population cohorts

Natural History

- Using electronic health record data and registry infrastructure:
- Describe the natural history of vaccine associated and non-vaccine associated myocarditis
- Identify risk factors at presentation influencing variability in clinical course including clinical details not available in larger administrative healthcare databases

Long Term Impact

- Within a hospital system research network:
- Describe the clinical course and assess possible long term sequelae of vaccine-associated myocarditis and myocarditis among unvaccinated patients over a 5 year period
- Incorporate prospective protocolized medical assessment and patient reported outcomes

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Signal Detection and Refinement

Current studies within the Risk Management Plan:

- **US Post-Authorization Safety Study (PASS) using HealthVerity data (mRNA-1273-P903)**
  - Status:
    - Ongoing quarterly reporting
    - Final analyses expected June 2023
    - ~50 million US residents with commercial, Medicare, or Medicaid coverage compared to 22.6 million Spikevax recipients

- **EU PASS (with VAC4EU) in Denmark, Norway, Italy, Spain and the United Kingdom (mRNA-1273- P904)**
  - Status:
    - Ongoing reporting every 6 months
    - Final results expected December 2023
    - ~30 million across 5 countries

- The US and European PASS are designed to characterize the risk of myocarditis and a large number of other Adverse Events of Special Interest specified by the EMA and FDA

- Bivalent vaccines will be considered in subgroup analyses in each study, as feasible. A dedicated study of bivalent vaccine safety is planned.

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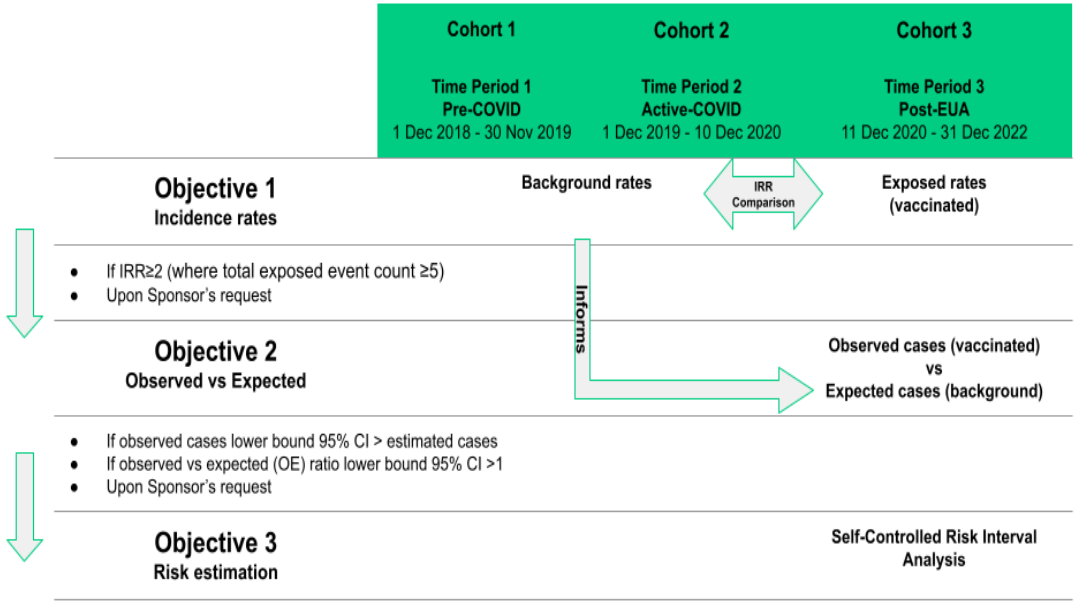
Ongoing: Secondary Database Study in HealthVerity (Study 903)

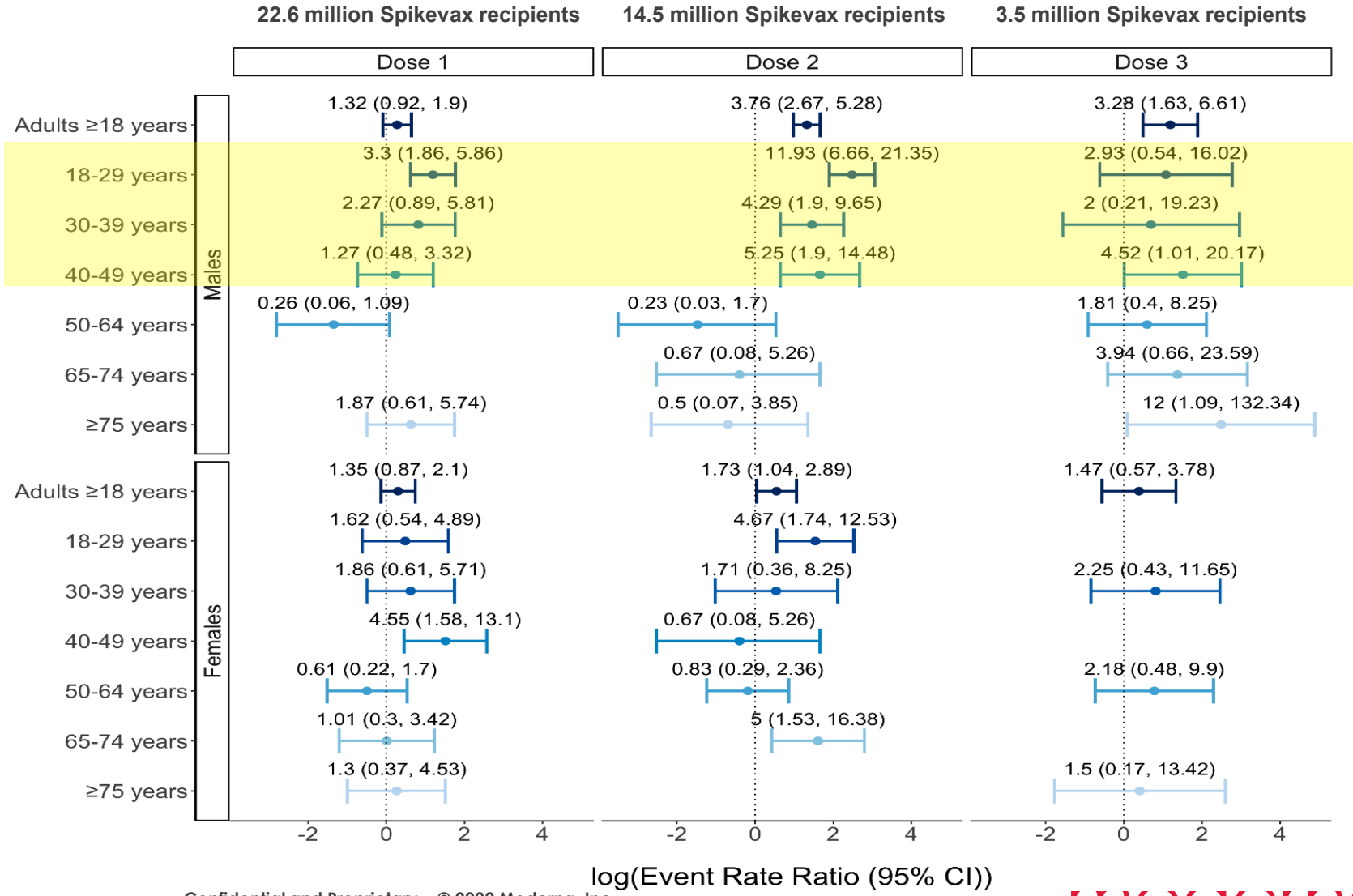
- **Analysis of HealthVerity data in collaboration with Aetion**
  - Large population (>22 million vaccine recipients) with longitudinal follow-up in administrative claims
  - Outcomes include myocarditis and other AESI (FDA and ACCESS)
- **Stages of analysis (*See figure*)**
  - Comparisons of post-vaccination event rates vs. historical event rates
  - Observed vs. expected analyses applying a relevant risk window after vaccination
  - Where a signal is observed, self-controlled risk interval analyses
- **Additional myocarditis supplemental analyses:**
  - Describe cases of myocarditis with respect to baseline characteristics and outcomes identifiable in administrative data
  - Refinement preliminary signals via SCRI analyses



US Post-Authorization Safety Study (PASS) using HealthVerity Data (Study 903) in >22 Million Vaccine Recipients*

Self-controlled risk interval analysis assessing myocarditis within 7 days of vaccination

- Data on myocarditis verify other findings in the published literature
- Numbers are still small for subgroup-specific estimates
  - e.g., only 6 cases (2 in risk window) in males 18-29 yrs. for dose 3



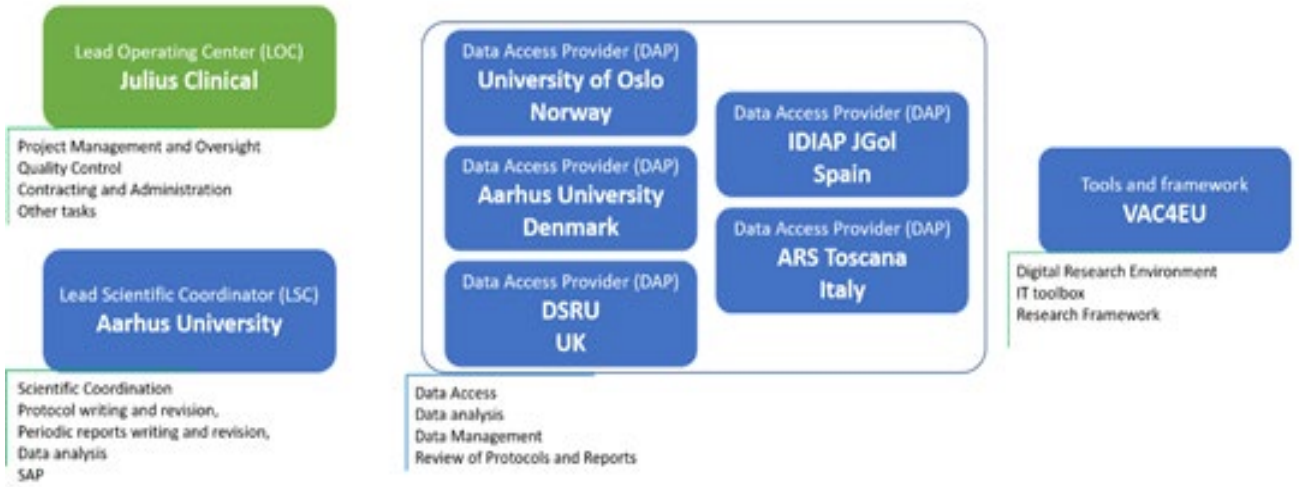
*April 2022 analyses

Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of Spikevax in Europe

Study mRNA-1273-P904

- Ongoing study mandated by the EMA
- The overarching research question of this study is whether the occurrence of adverse events of special interest (AESI) among persons vaccinated with COVID-19 Vaccine Moderna in Europe is higher than expected.
- Objectives and outcomes mirror the US PASS study, with estimation of incidence rates and risk ratios assessed in multiple subgroups:
  - Women of childbearing age
  - Patients who are immunocompromised
  - Patients previously diagnosed with COVID-19 infection
  - Patients with unstable health conditions and morbidities
  - Patients with autoimmune or inflammatory disorders
  - Age-specific populations (children, adolescents, adults)
- Next interim analyses expected March 2023, final analyses December 2023

VAC4EU
VAccine monitoring Collaboration for Europe



Country	Data updated on	N Spikevax doses* administered
Denmark	28 January 2022	1,681,529
Italy	13 February 2022	32,373,380
Norway	04 February 2022	2,233,155
Spain	11 February 2022	22,637,400
United Kingdom	16 February 2022	12,000,000

*As the same person may receive more than one dose, the number of doses is higher than the number of people in the population. (Source (Denmark, Italy, Norway, Spain: https://ourworldindata.org/covid-vaccinations "Which vaccines have been administered in each country?"(2); Source (UK): gov.uk (12), approximate number of doses, incl. 8.9 mi booster doses).

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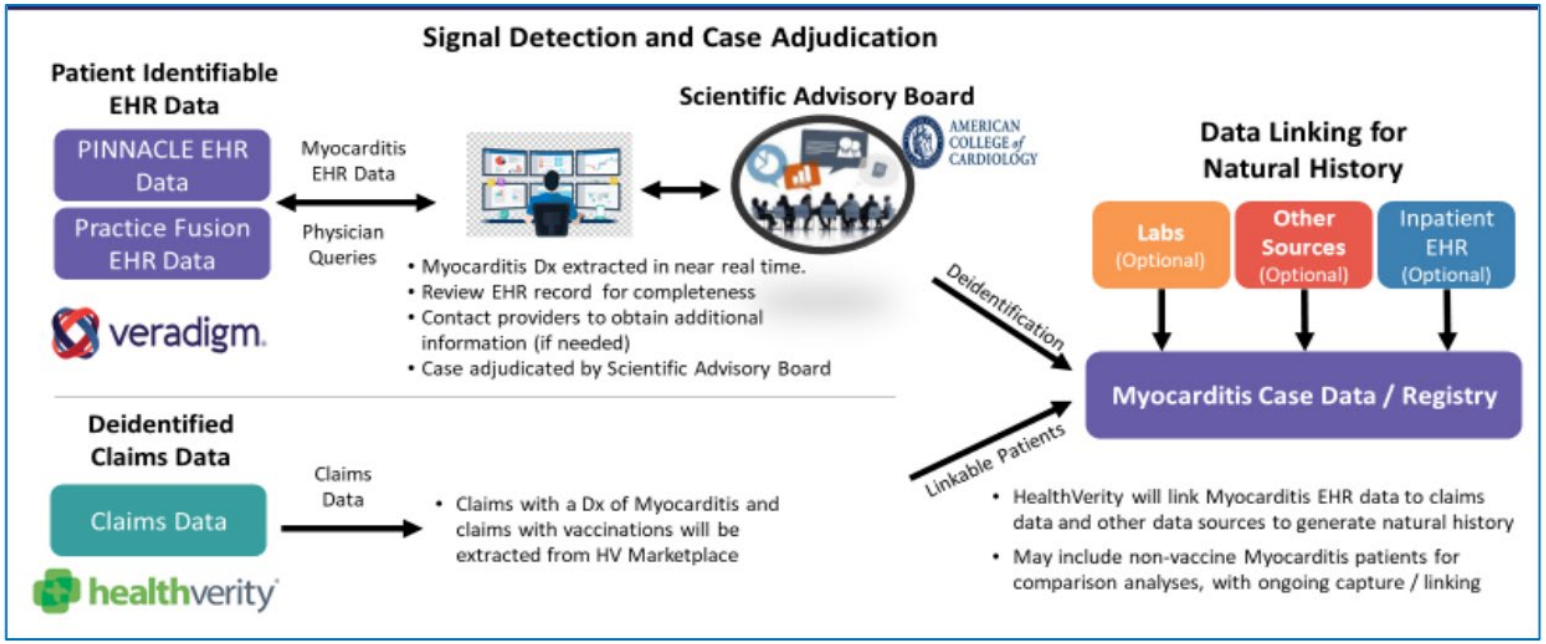
Long-term Outcomes of Myocarditis following Administration of SPIKEVAX

Study mRNA-1273-P911

- Planned analyses to:
  - Characterize presentation, clinical course, long-term sequelae of post-vaccine myocarditis, and functional outcomes
  - Compare long-term effects of post-vaccine myocarditis with those of nonvaccine myocarditis, including myocarditis arising in COVID-infected individuals
  - Identify possible risk factors for adverse long-term outcomes of post-vaccine myocarditis
- Monitoring cohort of > 300 cases of vaccine associated myocarditis adjudicated by cardiologists from ACC for up to 5 years to characterize long-term outcomes
- *Study is ongoing through October 2028 with annual interim analyses*.



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Executive Summary

- Moderna has implemented a comprehensive risk mitigation and characterization program for myocarditis/pericarditis associated with its monovalent and bivalent COVID-19 vaccines
- Clinical program: Informed consent and Investigator's Brochure updates, Cardiac Event Adjudication Committee, Biobanking
- Real world evidence program supplements routine pharmacovigilance
  - Incidence, risk characterization, and natural history
- After > 1.5 billion doses of Moderna COVID-19 (Monovalent and Bivalent) distributed, post-vaccine associated myocarditis cases
  - Very rare, follow age and gender distribution of viral myocarditis in pre-COVID era
  - Risk greatest after dose 2 of monovalent vaccine; additional risk factors have not yet been identified
  - Immunopathogenesis not yet understood
  - Benefit-risk for vaccination with SPIKEVAX is favorable

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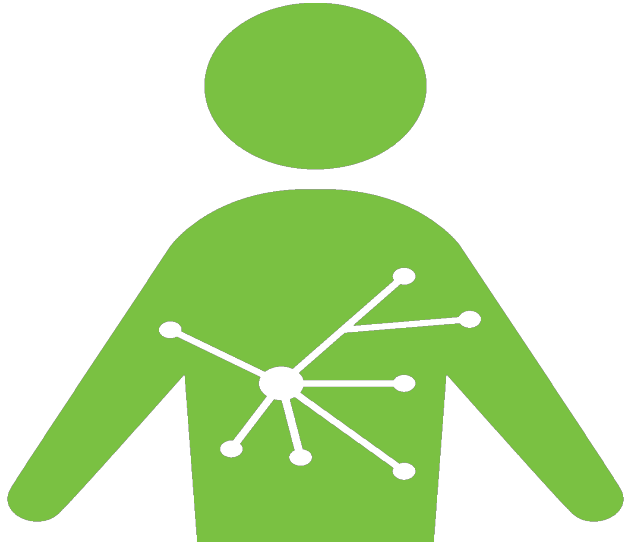

Thank you