Using Vaccine Ontology to Analyze and Integrate Vaccine Terms in N3C Dataset

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Background

The National COVID Cohort Collaborative (N3C) dataset[1], one of the largest and most detailed collections of electronic health record (EHR) data related to COVID-19 patients, encompasses diverse patient information across the USA dating back to 2018. It also enables COVID-19 vaccine studies with rich vaccination records. N3C employs the Observational Medical Outcomes Partnership Common Data Model (OMOP CDM)[2] as its basic infrastructure. However, the vast and heterogeneous nature of the N3C dataset presents significant challenges for integrating and analyzing specific vaccine terms. Although leveraging CVX[3], RxNorm[4], and RxNorm Extension[5] codes to standardize vaccine-related concepts, these terminologies lack robust semantic relations and proper hierarchy, leading to ineffective and discrepancy in the vaccine-related research[6,7].

The Vaccine Ontology (VO)[8,9] is a community-based biomedical ontology that provides a systematic ontological representation of vaccine terms with wide coverage and proper hierarchy. The VO facilitates the consistent annotation and integration of vaccine-related data, so it can serve as a backbone to integrate vast and heterogeneous vaccine vocabularies. In this study, we investigate the coverage of vaccine records in N3C by mapping these records to the VO and demonstrating how the VO can support more advanced data classification and analysis.

Method

1. Extraction of COVID-19 vaccine data from N3C

Based on the current designated hierarchy of Athena[10] and standard vocabulary, we first used concept '*947817:covid-19 vaccines; systemic*' as the highest level ancestor term of COVID-19 vaccines terms to retrieve all COVID-19 vaccine records. The used SQL code is shown as follows.

```
WITH cte_covid_vaccine AS
( SELECT b.*
FROM concept_ancestor a JOIN concept b ON a.descendant_concept_id = b.concept_id
AND a.ancestor_concept_id = 947817 )
SELECT drug_concept_id, drug_concept_name, vocabulary_id, COUNT(*) AS counts
FROM drug_exposure a JOIN cte_covid_vaccine b ON a.drug_concept_id = b.concept_id
GROUP BY drug_concept_id, drug_concept_name, vocabulary_id;
```

In addition, we used wildcards to retrieve COVID-19 vaccine terms as a comparison to see if any records are uncaptured. The used code is shown as follows.

```
SELECT drug_concept_id, drug_concept_name, vocabulary_id, COUNT(*) AS counts
FROM drug_exposure a
```

WHERE drug_concept_name like '%COVID-19%vaccine%'

GROUP BY drug_concept_id, drug_concept_name, vocabulary_id;

All data were accessed on June 12, 2024 on N3C enclave. A data quality check was executed to check for missing value and outliers. All qualified vaccine records data was included regardless of brands, platforms, variants, and time of administration. Then we collected and classified terms.

2. **Mapped vaccine terms to VO**

All collected vaccine terms were mapped to VO and then classified, analyzed based on VO pattern. One-to-one exact mapping was employed throughout the process, which means that for any single term, there is one and only one VO term mapped to it with the same gratuity and semantic content. No uphill or downhill mapping was allowed. So we might add new VO terms if necessary corresponding to a nonexisting vaccine term. To support terminology-specific annotations in VO, specific annotation properties, including 'RxNorm ID', 'RxNorm Extension ID', and 'OMOP concept ID', among others, were later added to VO to represent the corresponding content. The Robot tool[11] and Protege-OWL editor[12] were used to edit and display the terms.

Results

1. Summary of vaccine records from N3C

After using the concept '947817:covid-19 vaccines; systemic' as the ancestor term of COVID-19 vaccines terms, 25,835,254 rows records were extracted, including 17 distinct COVID-19 vaccine terms. All 17 terms were from RxNorm. While using wildcards in script, 27,371,805 rows were extracted, including 36 different COVID-19 vaccine terms, including 31 terms of RxNorm, 3 of CVX and 1 of RxNorm Extension. Consequently, the wildcards methods extracted 1,536,560 more rows of data than using the concept '947817:covid-19 vaccines; systemic' as the ancestor term.

Table 1 lists the top ten most frequently identified terms with detail. 'SARS-CoV-2 (COVID-19) vaccine, mRNA-BNT162b2 0.1 MG/ML Injectable Suspension' was the most frequent COVID-19 vaccine term in N3C.

Table 1. **Top 10 RxNorm COVID-19 Vaccine Concepts Based on Record Counts**

Ranking	OMOP_concept_id	OMOP_concept_name	Vocabulary	Counts	VO_ID
1	37003436	SARS-CoV-2 (COVID-19) vaccine, mRNA-BNT162b2 0.1 MG/ML Injectable Suspension	RxNorm	7,913,175	VO:0020221
2	1759206	SARS-CoV-2 (COVID-19) vaccine, mRNA-BNT162b2 0.1 MG/ML Injectable Suspension [Comirnaty]	RxNorm	7,141,808	VO:0020222
3	37003518	SARS-CoV-2 (COVID-19) vaccine, mRNA-1273 0.2 MG/ML Injectable Suspension	RxNorm	5,405,988	VO:0020206
4	779679	SARS-CoV-2 (COVID-19) vaccine, mRNA-1273 0.2 MG/ML Injectable Suspension [Spikevax]	RxNorm	1,290,092	VO:0020207
5	1525538	SARS-CoV-2 (COVID-19) vaccine, mRNA-BNT162b2 0.05 MG/ML / SARS-CoV-2 (COVID-19) vaccine, mRNA-BNT162b2 OMICRON (BA.4/BA.5) 0.05 MG/ML Injectable Suspension	RxNorm	1,012,279	VO:0020217
6	702118	SARS-CoV-2 (COVID-19) vaccine, mRNA-BNT162b2 0.05 MG/ML Injectable Suspension	RxNorm	793,039	VO:0020216

Ranking	OMOP_concept_id	OMOP_concept_name	Vocabulary	Counts	VO_ID
7	724904	SARS-COV-2 (COVID-19) vaccine, UNSPECIFIED	CVX	703,050	VO:0006704
8	37003432	SARS-CoV-2 (COVID-19) vaccine, mRNA spike protein	RxNorm	650,716	VO:0020194
9	1525543	SARS-CoV-2 (COVID-19) vaccine, mRNA-1273 0.05 MG/ML / SARS-CoV-2 (COVID-19) vaccine, mRNA-1273 OMICRON (BA.4/BA.5) 0.05 MG/ML Injectable Suspension	RxNorm	533,834	VO:0020201
10	739906	SARS-COV-2 (COVID-19) vaccine, vector - Ad26 100000000000 UNT/ML Injectable Suspension	RxNorm	515,887	VO:0020227

2. VO-based analysis of N3C vaccine records after vaccine term mapping

Figure 1 shows how the VO represents the hierarchical structure of the vaccines with records in N3C. Our study found clearer relations among these vaccine terms. For example, the RxNorm vaccine term: *'0.5 ML SARS-CoV-2 (COVID-19) vaccine, mRNA-1273 OMICRON (XBB.1.5) 0.1 MG/ML Injection'* is classified as the parent of another vaccine, *'0.5 ML SARS-CoV-2 (COVID-19) vaccine, mRNA-1273 OMICRON (XBB.1.5) 0.1 MG/ML Injection [Spikevax 2023-2024]'*. The latter term has the brand name 'Spikevax', while the other does not. Each of these vaccines is associated with specific N3C records (Figure 1). In addition to the "Injection" dose form, we also identified another dose form, "Prefilled Syringe", with the same vaccine ingredient and dose strength (i.e., concentration) (Figure 1).

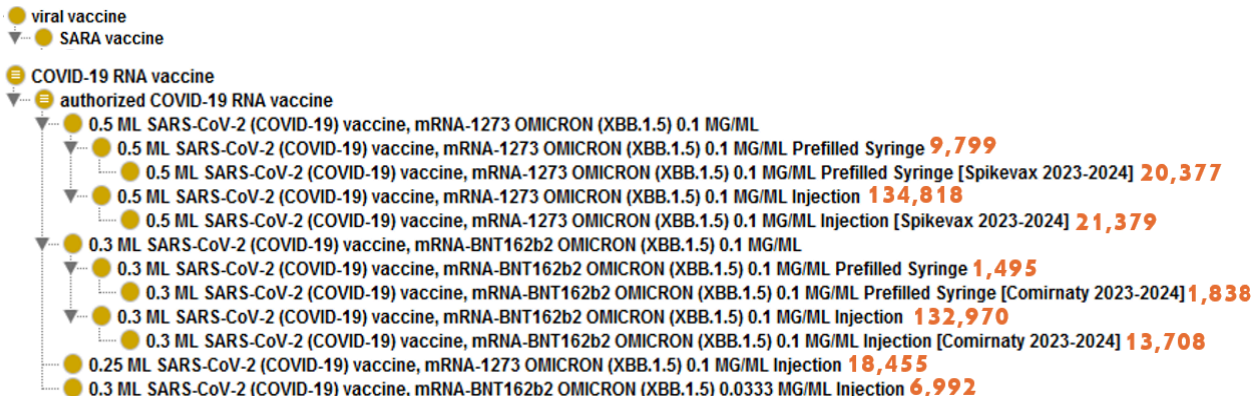

Figure 1. An example of VO hierarchical structure of the vaccines with N3C records. Protégé-OWL editor was used for ontology visualization. The numbers represent the counts of vaccine records in N3C.

Figure 2 shows a Description Logic (DL)-query that queries for all XBB.1.5-containing COVID-19 vaccines recorded in the N3C specific VO OWL file. XBB.1.5 is the latest subvariant of the Omicron variant of SARS-CoV-2 virus. Vaccines targeting XBB.1.5 have been available on the market since September 23, 2023[13]. The VO represents the information of the pathogen that a vaccine targets, so XBB.1.5 containing COVID-19 vaccines were queried using the following axiom:

'*immunizes against pathogen*' some 'SARS Coronavirus 2 *XBB.1.5*'

Overall, our DL-query identified 11 specific XBB.1.5-containing COVID-19 vaccines (Figure 2). Similarly, SPARQL can be used to perform such a query (data not shown). These queries demonstrate that the VO supports more advanced data analysis of N3C vaccine studies.

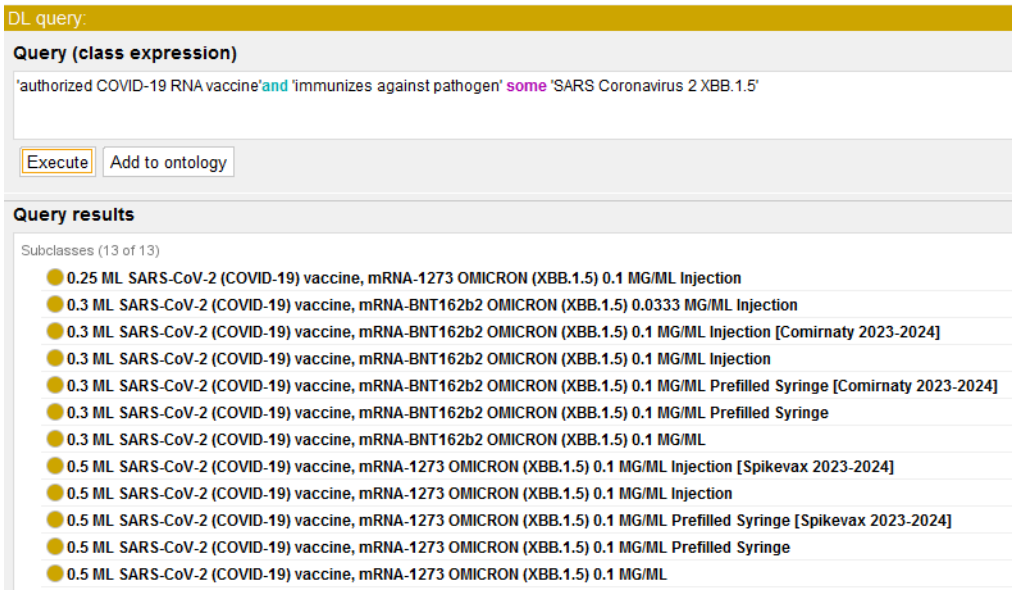

Figure 2. DL-query of XBB.1.5 containing COVID-19 vaccines

Conclusion

The vaccines recorded in the N3C dataset were mapped to and then analyzed using the VO. Our study shows that the VO improves semantic classification and applications of vaccine records in N3C, leading to more advanced data query and analysis.

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Ethics Approval

The N3C Data Enclave is managed under the authority of the NIH. Data transferred to the National Center for Advancing Translational Sciences (NCATS) from N3C is conducted under a Johns Hopkins University Reliance Protocol (IRB00249128) or individual site agreements with NIH. Data usage of this study was authorized by N3C (DUR-36ED2AE) and had been reviewed and approved by the Medical School Institutional Review Board (IRB) at the University of Michigan (HUM00243962).

Contributorship statement

YP was responsible for data generation, analysis and writing the first version of the manuscript. YH initiated the project and provided the original project design. JZ is an ontology expert. YHe served as the vaccine domain expert.

Competing interests

There are no competing interests for any author.

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Disclaimer

The N3C Publication committee confirmed that this manuscript msid:1834.309 is in accordance with N3C data use and attribution policies; however, this content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the N3C program.

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