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Anthrax Post-Exposure Prophylaxis Implementation Guide

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Record of Changes

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Table of Contents

1. Introduction	1
1.1 Background	1
1.2 Importance of Clinical Decision Support and this Clinical Decision Support Artifact	2
1.3 Audience, Purpose, and Scope of This Implementation Guide	2
2. Implementing and Using This Artifact	4
2.1 Description and Purpose of the Artifact	4
2.2 Summary of the Clinical Statement	4
2.3 Primary Use Cases	6
2.4 Recommendations and Suggested Actions	7
3. Guideline Interpretation and Clinical Decisions	10
4. Information for Clinicians Using the CDS	11
5. Artifact Manifest	12
5.1 Clinical Quality Language Library Relationship Diagram	12
5.2 Clinical Quality Language Dependency Graph	13
5.3 Additional Documentation	14
6. Testing	15
7. Implementation Checklist	16
8. Potential Reuse Scenarios	18
9. General Information about Clinical Quality Language	19
10. Integration with the Electronic Health Record	20
10.1 Clinical Quality Language Execution	20
10.2 Resource Mapping	20
Appendix A. Decision Log	22
A.1 Clinical Decision Support Artifact Semi-Structured Logic	22
A.2 Concept Definitions from the Semi-Structured Logic	25
A.3 Clinical Decision Support Artifact Development Decision Log	28
Acronyms	33
List of References	34

List of Figures

Figure 1. Relationship between Main Clinical Quality Language File and Existing Clinical Quality Language Libraries	13
Figure 2. Anthrax Post-Exposure Prophylaxis Clinical Quality Language Dependency Graph ..	14
Figure 3. Knowledge Level of Anthrax Post-Exposure Prophylaxis Clinical Decision Support Artifact (image source: https://cds.ahrq.gov/cdsconnect/about).....	16
Figure 4. Table showing types and versions of the FHIR resources generated by the CDS artifact.	18

List of Tables

Table 1. Clinical Decision Support Artifact Manifest	12
Table 2. Semi-structured Inclusion and Exclusion Logic	22
Table 3. Semi-structured Clinical Decision Support Intervention Logic	22
Table 4. Semi-structured Logic Concept Definitions	25
Table 5. Structured Artifact Decision Log.....	28

1. Introduction

The Centers for Disease Control and Prevention (CDC) sponsored a project to help generate a systematic and replicable process for transforming clinical guidelines into shareable and standards-based clinical decision support (CDS) artifacts. To execute the project, CDC engaged the CMS Alliance to Modernize Healthcare federally funded research and development center (the Health FFRDC). The use case for this project was to provide standardized, consistent, and computable guidance to health care systems during a wide-area aerosol release of *Bacillus anthracis* spores in the United States.

A CDS artifact is a template for defining how clinical decision support is provided for a given clinical situation, often including triggers, logic, operations, recommendations and actions, and supporting evidence. To understand the complexities of translating guidelines into actionable CDS for integration into local Electronic Health Record (EHR) systems during a potential public health emergency, we developed CDS for post-exposure prophylaxis (PEP) for inhalation anthrax. We created a care flow diagram to clarify how the CDC anthrax guidelines would work in a CDS tool. The care flow diagram also helped identify the data elements required to express CDS using the interoperable Health Level 7 (HL7) Clinical Quality Language (CQL) [1] and leveraging a Fast Healthcare Interoperability Resources (FHIR) [2] data model. Given the paucity of anthrax cases in the United States, we tested the CDS tool using synthetic patient records. However, we identified tasks for local health system adaptation and implementation of the CDS tool. A systematic process was followed that included developing an evaluation framework, applying the evaluation framework during a review of multiple CDC anthrax guidelines, selecting specific treatment recommendations, developing the care flow process, identifying the data required to express the concepts in CDS, translating the CDS into CQL, conducting a simulated pilot, and verifying the results. Throughout this process, we documented issues and proposed solutions, decisions, and lessons learned.

1.1 Background

During both the Ebola virus outbreak in 2014 and the Zika virus outbreak in 2016, clinical guidance and recommendations for testing and treatment were changing rapidly as data became available. In both instances, public health authorities disseminated guidance and recommendations to healthcare providers in near real time but not in a standardized, machine-readable format that could be readily integrated into EHR systems. While there was an attempt to do so during the Zika response, a process to rapidly and accurately translate guidance and recommendations into CDS tools had not yet been established.

CDC kicked off a multi-stakeholder initiative in February 2018, Adapting Clinical Guidelines for the Digital Age (herein referenced as Digital Age initiative), to elucidate the following five key steps in the continuum from guideline creation through guideline evaluation: Guideline Creation / Summarizing the Evidence, Informatics Framework for Guideline Creation, Dissemination Tools and Communication Methods, Translation and Implementation Support, and Evaluation.

This project was initiated to explicate the complexities of translating guidelines into actionable CDS tools for integration by local EHR systems during a potential public health emergency and to document lessons learned for the Digital Age initiative. The use case was for PEP for inhalation anthrax. The use case focused on adults with non-occupational exposure to *Bacillus*

anthracis who are asymptomatic and not previously vaccinated. The goal was to document a reproducible process for translating clinical guidelines into executable formats for integration into local EHR systems.

1.2 Importance of Clinical Decision Support and this Clinical Decision Support Artifact

As previously stated in the background, during the Ebola and Zika virus outbreaks, critical guidance and recommendations from public health authorities were not available in a standardized, machine-readable format that could be readily integrated into EHR systems. When combining multiple sources of guidance and recommendations, it is difficult and time consuming for individual health care systems to analyze and translate the information into a machine-readable format and multiple interpretations could result.

Clinical decision support expressed as executable artifacts based on industry standards can improve public health outcomes by enabling the following:

- Enhanced consistency across implementation sites
- Enhanced precision in guideline implementation
- Reduced redundancy at implementation level
- Reduced translation time from bench to bedside

This CDS artifact translates multiple CDC guidelines and clinical guidance into machine executable standards-based format for use in an anthrax emergency. It is important to note that although an anthrax incident is rare, the impact of such is significant. Well-timed and effective PEP, as reflected in this CDS artifact, can potentially save thousands of lives. It is essential to start PEP of asymptomatic persons as soon as possible after exposure because its effectiveness decreases with delay. The combined use of an antimicrobial drug for immediate protection and a 3-dose series of anthrax vaccine for long-term protection is essential. Health care systems integrating this CDS artifact into their current EHRs would be prepared to respond in the event of an inhalation anthrax emergency.

1.3 Audience, Purpose, and Scope of This Implementation Guide

This document is intended to provide information about the development, implementation, and routine operation of the “Anthrax Post Exposure Prophylaxis” (“Anthrax PEP”) CDS artifact. Various audiences may find this information helpful, including:

1. **Public Health (Administrators and Clinicians)** responsible for overseeing the management of individuals exposed to inhalation anthrax in a bioterrorism event or other such act.
2. **Clinicians and Leaders** at healthcare organizations in preparation for an inhalation anthrax event who wish to implement, test, and execute CDS related to this topic in their EHRs or other health information tools.
3. **CDS Developers and Informaticists** who may have suggestions, additions, or seek to add CDS artifacts on similar topics, or who want to make use of well-developed structured logic and CQL in their own work. Additionally, it would be useful to groups in developing artifacts addressing other aspects of care for persons exposed to

anthrax, such as children under 18 years of age and treatment for diagnosed anthrax (e.g., cutaneous, inhalation).

4. **Organizations or Individuals** interested in developing their own CDS artifacts might find this document helpful as a resource for the process by which clinical guidelines are translated into mature CQL artifacts.

2. Implementing and Using This Artifact

2.1 Description and Purpose of the Artifact

This CDS artifact provides initial screening for adults ≥ 18 years of age exposed to anthrax during a bioterrorism event to determine if the individual has signs or symptoms consistent with anthrax. The CDS artifact provides post-exposure prophylaxis for asymptomatic adults, including pregnant women, for both antimicrobial therapy and vaccine. The artifact is a CDS rule representation of CDC clinical guidance for antimicrobial therapy and anthrax vaccine.

CDC anthrax clinical guidance was provided primarily in narrative format and technical tables published in peer-reviewed journals. The reviewed guidelines contained no specific, graded recommendation statements, and the CDS artifact was not directly derived from any one guideline. This CDS artifact represents CDC-published anthrax guidance from the sources listed below to inform the care flow for clinical decision making.

2.2 Summary of the Clinical Statement

This CDS artifact is based on the guidance in the following resources:

- Ciprofloxacin for Post-Exposure Prophylaxis of Anthrax: Emergency Use Instructions for Healthcare Providers [3]
- Doxycycline for Post-Exposure Prophylaxis of Anthrax: Emergency Use Instructions for Healthcare Providers [4]
- Centers for Disease Control and Prevention Expert Panel Meetings on Prevention and Treatment of Anthrax in Adults [5]
- Centers for Disease Control and Prevention Expert Panel Meetings on Prevention and Treatment of Anthrax in Adults: Technical Appendix [6]
- Special Considerations for Prophylaxis for and Treatment of Anthrax in Pregnant and Postpartum Women [7]
- Special Considerations for Prophylaxis for and Treatment of Anthrax in Pregnant and Postpartum Women: Technical Appendix [8]
- Use of Anthrax Vaccine in the United States: Recommendations of the Advisory Committee on Immunization Practices (ACIP) [9]

Standard methods such as the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) method [10] were not used to rate the quality of the recommendations or guidance.

For contextual awareness, key components of the CDS artifact were derived from the following:

- If patient has signs or symptoms consistent with anthrax, a full diagnostic evaluation for anthrax must occur. The signs and symptoms listed in this CDS are from the Public Health Information Network Vocabulary Access and Distribution System (PHIN VADS) PHVS_SignsSymptoms_Anthrax value set [11] and CDC anthrax guidelines in the reference list [5] [6] [7] [8] [9]. They were approved by anthrax subject matter experts (SMEs) from the Bacterial Special Pathogens Branch, Division of High-Consequence

Pathogens & Pathology, National Center for Emerging and Zoonotic Infectious Diseases, CDC (hereafter referred to as “CDC anthrax SMEs”) (2018, personal communication). The anthrax signs and symptoms listed are those most commonly related to inhalation, gastrointestinal, and cutaneous anthrax; however, the list is not exhaustive. If a patient does *not* have any signs or symptoms consistent with anthrax, the patient is considered asymptomatic. The second part of the CDS is triggered by the asymptomatic code.

- PEP should be used for previously unvaccinated persons ≥ 18 years of age after exposure to aerosolized *Bacillus anthracis* spores, whether the exposure is naturally occurring, occupationally related, or intentional. To elicit the most substantial and rapid immune response possible for previously unvaccinated persons in a post-exposure setting, vaccination should be administered as recommended in conjunction with appropriate antimicrobial agents [9]. The vaccine is administered as three doses 14 days apart [9].
- Antimicrobial drugs are an essential component of PEP [5] [6] [7] [8]. Ciprofloxacin, levofloxacin, and doxycycline are Food and Drug Administration (FDA) approved for the antimicrobial drug portion of PEP for inhalation anthrax in adults ≥ 18 years of age regardless of penicillin susceptibility or if susceptibility is unknown [5]. No safety data is available for levofloxacin use beyond 30 days; thus, oral ciprofloxacin and doxycycline are recommended as first-line antimicrobial drugs for PEP [5]. Alternative antimicrobial medications that could be used if the first-line agents are not tolerated or are unavailable are levofloxacin, moxifloxacin, and clindamycin [5].
- A key distinction in pregnancy is that ciprofloxacin is preferred over doxycycline for first-line PEP [7]. Pregnant women at risk for inhalation anthrax should receive anthrax vaccine and antimicrobial drug therapy regardless of pregnancy trimester [7].

Of note the following are suggested as cautions in using this artifact:

- BioThrax (anthrax vaccine) is FDA approved and indicated for active immunization for the prevention of disease caused by *B. anthracis* in persons 18–65 years of age when administered in conjunction with recommended antimicrobial drugs. It should be avoided by individuals with a history of anaphylactic or anaphylactic-like reaction following a previous dose of BioThrax (anthrax vaccine) or any component of the vaccine.
- If BioThrax (anthrax vaccine) is used during pregnancy, or if the patient becomes pregnant during the vaccination series, the patient should be apprised of the potential hazard to the fetus.
- This represents the combination of multiple guidelines which are periodically updated with input from CDC anthrax SMEs. This artifact was created from multiple guidelines and data provided and verified with CDC anthrax SMEs in 2018.
- An antimicrobial medication is displayed as an option for providers even if the patient has a documented allergy to that medication, with an alert to indicate the allergy. In the event of anthrax exposure due to a bioterrorism event, the allergy might be not an absolute contraindication to a first-line medication regimen. Clinicians should evaluate the allergy prior to determining the appropriate antimicrobial medication.
- Included is a list of potential signs and symptoms of anthrax derived from the CDC PHIN VADS value set 'PHVS_SignsSymptoms_Anthrax' and from CDC anthrax guidelines. The list is not exhaustive; key signs and symptoms to alert the provider that the patient

may be symptomatic to prompt further diagnostic evaluation are included. The artifact is intended for asymptomatic patients.

- Individuals who have had a full BioThrax (anthrax vaccine) series for pre-exposure prophylaxis might need a booster dose following anthrax exposure. This CDS artifact does not include booster doses of BioThrax (anthrax vaccine) for persons who have completed a pre-exposure vaccination series.

2.3 Primary Use Cases

In the primary use case, the CDS artifact is intended for use by clinicians delivering care in an outpatient setting. In the event of a bioterrorism attack, CDC assumes that PEP would be provided primarily at outpatient settings called Points of Dispensing (PODs) rather than in routine clinical settings. However, persons might seek care outside of PODs for initial and follow-up care, and PODs might not be available in all geographic areas or during the early part of a response. Therefore, persons with exposure to anthrax might seek care in routine outpatient settings. The clinical use case is particularly relevant to clinicians specializing in Emergency Medicine, Family Medicine, Internal Medicine, Obstetrics and Gynecology, and Preventive Medicine.

The CDS artifact presents a sequential process for determining if the person meets the applicable age requirements, was exposed to anthrax within the previous 60 days, and is asymptomatic (i.e., has no signs or symptoms consistent with anthrax). If the person meets these criteria, the CDS tool provides the PEP antimicrobial treatment and vaccine series, with a slight variation in PEP antimicrobial treatment for pregnant women. It is useful for persons at any point in the care flow process, from determining anthrax exposure through the completion of the anthrax vaccine series.

1. When deciding whether to initiate PEP in persons exposed to anthrax.

- A. Dr. Alpha is presented with a patient who states that he/she was exposed to anthrax. Dr. Alpha is determining whether to initiate PEP. He reviews the exposure history, documents exposure to anthrax, and assesses the patient for signs and symptoms of anthrax. He determines that the patient has *difficulty breathing, stridor, and dyspnea*. Dr. Alpha decides to initiate diagnostic testing to determine if the patient has anthrax.
- B. Dr. Alpha is presented with a patient who states that he/she was exposed to anthrax. Dr. Alpha is determining whether to initiate PEP. He reviews the exposure history, documents exposure to anthrax, and assesses the patient for signs and symptoms of anthrax. He determines that the patient has *none of the signs and symptoms of anthrax* and documents that the patient is asymptomatic. Dr. Alpha initiates PEP for the patient.

2. When deciding whether to initiate PEP in asymptomatic persons exposed to anthrax.

- A. Dr. Jones is presented with a patient who has a validated exposure to anthrax, exposure was 20 days ago, patient is asymptomatic, and *has not received any care*

for the exposure. She discovers the patient has a prescription for ciprofloxacin 500 mg once per day for 30 days. Dr. Jones determines that this is not an adequate dosage for anthrax PEP. She prescribes 30 additional days of ***ciprofloxacin 500 mg orally every 12 hours*** to ensure the recommended 60-day regimen is provided.

Additionally, she would assess for history of anthrax vaccine since the exposure and latex allergy, and if none, she ***prescribes administration of anthrax vaccine.***

- B.** Dr. Jones is presented with a patient who has a validated exposure to anthrax, exposure was 30 days ago, patient is asymptomatic, ***and has not received any care for the exposure.*** The patient is not on any of the antimicrobials and has not received any anthrax vaccinations. She determines that the patient has an allergy to both ciprofloxacin and doxycycline. Questioning the patient about the allergies, she learns they were both minor skin rashes. Since these two antimicrobials are the first-line medications for anthrax PEP and the patient does not have any of the indicated cautions or contraindications for the first-line medications ***except a minor skin rash, she initiates antimicrobial treatment,*** providing one of the first-line medications (i.e., ciprofloxacin or doxycycline) according to the recommended dose of ciprofloxacin 500 mg by mouth every 12 hours for 60 days or doxycycline 100 mg by mouth every 12 hours for 60 days. (Note: If the patient was pregnant, Dr. Jones would prioritize the first-choice medication, ciprofloxacin.) She provides the patient education about the medication prescribed and instructions on how to address any allergic reactions. She would also assess for history of anthrax vaccine since the exposure and latex allergy, and if none, she ***prescribes administration of anthrax vaccine.***
- C.** Dr. Jones is treating a patient who states that he/she was exposed to anthrax, is currently taking antimicrobials for PEP for 60 days and is ***returning for an anthrax vaccine.*** The patient received an anthrax vaccine following exposure. She determines which vaccination in the series the patient requires, whether the required time from the last vaccine administration has elapsed, and ***prescribes administration of anthrax vaccine.***

2.4 Recommendations and Suggested Actions

The detailed CDS is available in “**Intervention(s) and Action(s)**” in the **Semi-Structured Representation** section. The structured representation of this CDS artifact supports the following:

1. Determine if the patient is greater than [$>$] = 18 years, if the patient has been exposed to anthrax within the past 60 days, and if the patient does not have a diagnosis of anthrax. If any of these criteria are not met, stop.
2. If these criteria are met, and there is not an asymptomatic code, post an alert with the signs and symptoms of anthrax and guidance to conduct a full diagnostic workup if any of the signs and symptoms are present. A patient with any sign or symptom consistent with anthrax must be fully evaluated and then treated if found to have anthrax.

3. If the patient is greater than [$>$] = 18 years, has been exposed to anthrax within the past 60 days, and is asymptomatic, the PEP CDS would be initiated as outlined below.
4. First, determine if the patient has been prescribed any of the first line (i.e., ciprofloxacin or doxycycline) or second-line (i.e., levofloxacin, moxifloxacin, clindamycin) antimicrobials. If the patient has an active prescription, display which medication and post an alert listing the required dosage, frequency, and duration required for PEP. For example, *“The patient has an active prescription for doxycycline. Evaluate the dosage and duration to ensure a 60-day regimen of appropriate antibiotic post-anthrax exposure: Doxycycline 100 mg by mouth every 12 hours for 60 days.”*
5. Address the first-line antimicrobials. Since one antimicrobial is preferred for pregnant patients, non-pregnant and pregnant patients are addressed separately.
 - a. If the patient is pregnant,
 - i. Determine if the patient is allergic to ciprofloxacin or doxycycline. If true, display which medication(s) the patient is allergic to and confirm allergy status.
 - ii. Display the ciprofloxacin and doxycycline PEP with appropriate contraindications, cautions, and additional instructions indicating ciprofloxacin as the first-choice antimicrobial and doxycycline as the second-choice antimicrobial in pregnancy.
 - iii. Display that pregnant women should receive PEP regardless of pregnancy trimester.
 - b. If the patient is not pregnant,
 - i. Determine if the patient is allergic to ciprofloxacin or doxycycline. If true, display which medication(s) the patient is allergic to and confirm allergy status.
 - ii. Display the ciprofloxacin and doxycycline PEP with appropriate contraindications, cautions, and additional instructions indicating ciprofloxacin and doxycycline are both first-line antimicrobials.
6. Next, address the second-line antimicrobials.
 - a. If the patient is pregnant,
 - i. Determine if the patient is allergic to levofloxacin, moxifloxacin, or clindamycin. If true, display which medication(s) the patient is allergic to and confirm allergy status.
 - ii. Display the levofloxacin, moxifloxacin, and clindamycin PEP with appropriate contraindications, cautions, and additional instructions indicating that all are second-line antimicrobials.
 - iii. Display that pregnant women should receive PEP regardless of pregnancy trimester.
 - b. If the patient is not pregnant,
 - i. Determine if the patient is allergic to levofloxacin, moxifloxacin, or clindamycin. If true, display which medication(s) the patient is allergic to and confirm allergy status.

- ii. Display the levofloxacin, moxifloxacin, and clindamycin PEP with appropriate contraindications, cautions, and additional instructions indicating all are second-line antimicrobials.
7. Address anthrax vaccine, BioThrax.
 - a. Determine if the patient is allergic to BioThrax (anthrax vaccine) and if so, post an alert indicating the allergy.
 - b. Determine if the patient is allergic to latex. If the patient is allergic to latex, indicate the allergy and a note highlighting that the stopper of the vial contains latex.
 - c. Determine if previous anthrax vaccinations are missing a date or if there is a missing or non-sequential anthrax vaccination, and if so, provide an alert indicating the discrepancy.
 - d. Determine which, if any, of the anthrax vaccines in the series the patient has received and the time since the last vaccine was administered.
 - i. If the patient has received the third or fourth anthrax vaccine, stop.
 - ii. If the patient has received the second but not the third anthrax vaccine and the required 14 days have passed since the last vaccine, then administer the third vaccine.
 - iii. If the patient has received the first but not the second anthrax vaccine and the required 14 days have passed since the last vaccine, then administer the second vaccine.
 - iv. If the patient has not received any anthrax vaccine, administer the first vaccine in the series.
 - e. If the patient is pregnant,
 - i. Display that pregnant women should receive the anthrax vaccine regardless of pregnancy trimester.

Future implementers may want to consider enhancing the existing code within their system to support the following suggested actions by the clinicians:

- If a patient is asymptomatic document that the patient is asymptomatic if patient does not present with signs and symptoms of anthrax. (This will trigger the next section of the artifact)
- If a patient has a current prescription for a recommended antimicrobial but dosage and duration are not consistent with recommendation, indicate the need to document that prior to initiating the medication.
- State to provide patient education on medications or vaccine and suggest/include a link for the provider to use.

3. Guideline Interpretation and Clinical Decisions

The five CDC anthrax guidelines represented in this CDS artifact all pertained to anthrax PEP recommendations, but with slightly different foci (i.e., vaccine, adult, pregnancy, and two first-line antimicrobials). The guidelines and clinical guidance were published at different times (i.e., vaccine in 2010; adult and pregnancy in 2014) and in different formats (emergency use instructions for antimicrobials in 2017). There were discrepancies in recommendations across the content. Thus, during the development of this CDS artifact, numerous decisions were made about the appropriate clinical content and structured CDS artifact representation. Appendix A explains, in detail, how terms were defined and decisions were made with a rationale for each. Some of the key interpretations and decisions include:

1. Whenever there was a conflict between guidelines, the latest version of guideline was used.
2. Conflicts were resolved with input from the CDC anthrax SMEs.
3. The guidelines did not offer any definitive guidance on what “if tolerated” represents. The CDS represents “if tolerated” as allergies and intolerances as described in Section 10.2; when pertinent allergies or intolerances are found in the patient electronic health record, a message is provided to “confirm allergy status” as a reminder to ask about previous reactions.
4. The documentation of allergies varies across EHR systems. RxNorm codes are the accepted standard (<https://www.healthit.gov/isa/representing-patient-allergies-and-intolerances-medications>). This CDS uses the overarching ingredient code for the antimicrobial therapy [12].
5. The most effective PEP antimicrobials must be considered even if the patient has a history of antimicrobial allergies. Based on the type and severity of a previous allergic reaction, the clinician might want to consider prescribing first-line antimicrobials for PEP to a patient because of the potential severity of inhalation anthrax, which includes death. Thus, antimicrobial options for PEP are presented in the CDS tool even if there is a documented allergy to the antimicrobial. There is a reminder to ask about allergies to assess the type and severity of the allergic reaction to determine the most appropriate antimicrobial therapy.

4. Information for Clinicians Using the CDS

Exposure to anthrax is rare in the United States (<1 case reported per year historically) [5]. However, anthrax has been associated with bioterrorism events. Anthrax is a serious infectious disease that can be fatal if not properly treated. PEP must be initiated in a timely manner and of sufficient duration to prevent disease. Anthrax disease will develop in patients who are not identified and provided with PEP. Appropriate clinical care at the initial stage of a response is crucial.

This CDS artifact addresses one component of the care process—PEP for asymptomatic patients exposed to anthrax. However, because monitoring care *over time* is important, this CDS artifact should be implemented within a care setting that is holistic and patient-centered, with informed and shared decision making to ensure successful outcomes [13]. Addressing two key aspects of the care process is especially important.

First, logistically, how will the patient be monitored and followed appropriately? For example, if the patient lives in a geographical region remote from the exposure site, what are the resources available to the patient upon returning home, how will these be coordinated, and with whom?

Second, because PEP requires 60 days of antimicrobial therapy and three vaccines administered at least 14 days apart, adherence is likely to be challenging. Thus, clinicians must address factors that influence adherence, such as knowledge of the disease; social and economic factors; patients' perceptions, motivations, and levels of physical and/or cognitive impairment; and issues related to the specific medication therapy [14]. Shared decision making is important to ensure that the patient understands the potential severity of anthrax disease and adheres to PEP to prevent a negative outcome, including death.

5. Artifact Manifest

Three versions of the “Anthrax Post-Exposure Prophylaxis” CDS artifact have been developed assuming the following data models: FHIR Draft Standard for Trial Use 2 (DSTU2) [15], FHIR Standard for Trial Use 3 (STU3) [16], and FHIR Release 4 [17]. Each version of the artifact can be considered a separate CQL library, and each is comprised of a number of files (see Table 1 below). These files are contained in a zip archive entitled “Anthrax_Post_Exposure_Prophylaxis_FHIR_CQL_Updated_7June2019”, which includes a detailed “README” text file with further information.

Table 1. Clinical Decision Support Artifact Manifest

Filename	Purpose	Author(s)
Anthrax_Post_Exposure_Prophylaxis_FHIRv102.cql Anthrax_Post_Exposure_Prophylaxis_FHIRv300.cql Anthrax_Post_Exposure_Prophylaxis_FHIRv400.cql	CQL representation of “Anthrax Post-Exposure Prophylaxis” CDS artifact. Specifies the logic necessary for querying patient records and returning the recommended PEP treatment.	Marc Hadley, David Winters
Anthrax_Post_Exposure_Prophylaxis_FHIRv102.json Anthrax_Post_Exposure_Prophylaxis_FHIRv300.json Anthrax_Post_Exposure_Prophylaxis_FHIRv400.json	Expression Logical Model (ELM) representation of “Anthrax Post-Exposure Prophylaxis” CDS artifact (see Section 10.1). Specifies the logic necessary for querying patient records and returning the recommended PEP treatment.	Marc Hadley, David Winters
CDS_Connect_Commons_for_FHIRv102.cql CDS_Connect_Commons_for_FHIRv300.cql CDS_Connect_Commons_for_FHIRv400.cql	Library of common CQL functions that may be called by other CDS artifacts.	Julia Afeltra, Chris Moesel, David Winters, Marc Hadley
CDS_Connect_Commons_for_FHIRv102.json CDS_Connect_Commons_for_FHIRv300.json CDS_Connect_Commons_for_FHIRv400.json	ELM representation of library of common CQL functions that may be called by other CDS artifacts.	Julia Afeltra, Chris Moesel, David Winters, Marc Hadley
CDC_Common_Logic_FHIRv102.cql CDC_Common_Logic_FHIRv300.cql CDC_Common_Logic_FHIRv400.cql	Library of commonly-used CQL functions specific to this CDC project.	David Winters, Marc Hadley
CDC_Common_Logic_FHIRv102.json CDC_Common_Logic_FHIRv300.json CDC_Common_Logic_FHIRv400.json	ELM representation of library of commonly-used CQL functions specific to this CDC project.	David Winters, Marc Hadley
FHIRHelpers.cql (DSTU2) FHIRHelpers.cql (STU3) FHIRHelpers.cql (R4)	Common CQL functions used to convert CQL data elements to FHIR and back again.	Bryn Rhodes
FHIRHelpers.json (DSTU2) FHIRHelpers.json (STU3) FHIRHelpers.json (R4)	ELM representation of common CQL functions used to convert CQL data elements to FHIR and back again.	Bryn Rhodes
LICENSES.txt	Describes intellectual property considerations for each CQL/ELM file.	David Winters
CDS_Connect_Commons_for_FHIRv300_Modifications.txt CDS_Connect_Commons_for_FHIRv400_Modifications.txt	Describes changes made to CDS Connect Commons library (FHIR STU3 and R4 versions only).	David Winters

5.1 Clinical Quality Language Library Relationship Diagram

The main CQL file for the Anthrax PEP CDS is entitled “Anthrax_Post_Exposure_Prophylaxis.” This main file leverages existing code in the form of other CQL libraries to help implement

common and repetitive aspects in the logic. Figure 1 below depicts this relationship using a diagram, and the included text files (“LICENSES” and “CDS_Connect_Commons_for_FHIRv***_Modifications”) describe the pedigree and licenses of the included libraries.

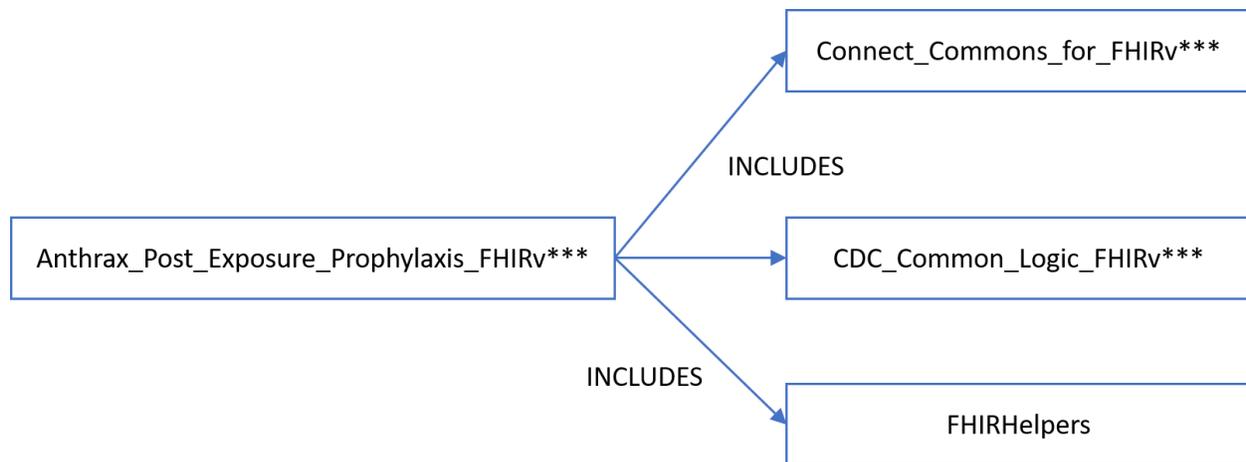


Figure 1. Relationship between Main Clinical Quality Language File and Existing Clinical Quality Language Libraries

5.2 Clinical Quality Language Dependency Graph

A CQL dependency graph depicts all codes, value sets, concepts, parameters, and expressions used by a CDS artifact and can provide a high-level view of the relationships between each of these elements. Relationships are depicted using a directed graphical approach, where arrows represent dependencies between elements in the CQL. A CQL dependency graph for the Anthrax PEP CQL is shown in Figure 2 below. As is evident from the figure, the Anthrax PEP CDS is a complex artifact that includes over a hundred CQL expressions and over two hundred dependencies.

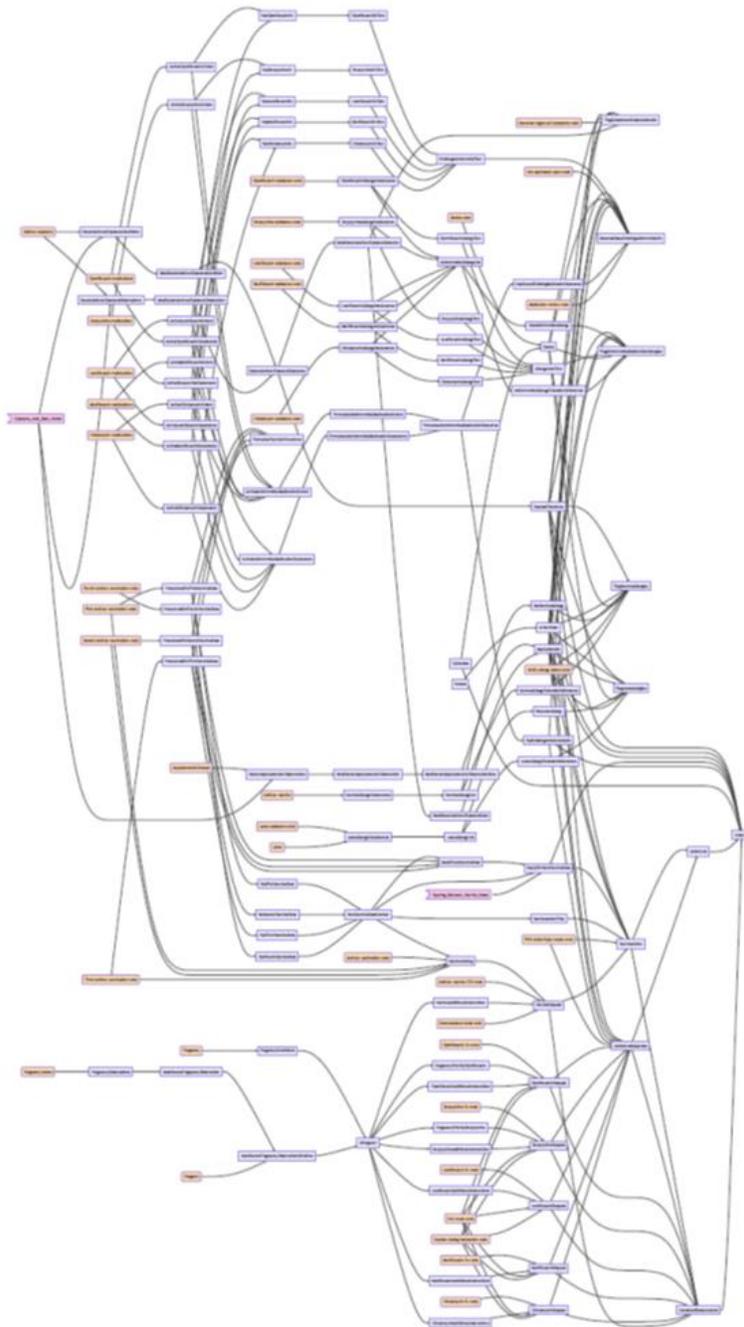


Figure 2. Anthrax Post-Exposure Prophylaxis Clinical Quality Language Dependency Graph

5.3 Additional Documentation

The zip archive “Anthrax_Post_Exposure_Prophylaxis_FHIR_CQL_Updated_7June2019” that includes the CQL files that comprise the artifact also includes a number of additional files which further describe the artifact. See Section 10.2 for more information.

6. Testing

The Anthrax PEP CQL was written using a test-driven development (TDD) approach [18]. With TDD, an iterative approach is taken whereby executable tests are written before the corresponding functionality exists in the software. These tests naturally fail at first, and only pass when enough software has been written to implement the functionality under test. Software written using a TDD approach is said to have fewer bugs since only enough software is written to ensure the desired functionality is implemented.

An automated testing framework written in Node.js [19] has been used to support a TDD approach of the Anthrax PEP CQL. This framework accepts test cases specified in YAML (a recursive acronym that expands to YAML Ain't Markup Language) [20]. Each test is specified in terms of an input synthetic patient record as well as the expected output from the CQL. The framework automatically loads each test, runs the CQL against the input synthetic patient records, and compares the actual and expected outputs from the CQL. If the actual and expected outputs from the CQL match, the test passes. If the actual and expected outputs do not match, the test fails.

Sixty-one automated tests were developed in the process of writing the Anthrax PEP CQL. Each test has been designed against specific aspects of the Anthrax PEP CQL. For example, the first test written input a synthetic patient who was older than 18 years of age, and the expected output required that the CQL correctly determine that the patient was indeed older than 18. The 61 YAML test files have been used together with the testing framework to generate JavaScript Object Notation (JSON) files containing the data inputs and expected outputs for each test. These JSON files are included in a zip archive entitled “Anthrax_Post_Exposure_Prophylaxis_Tests_Updated_7June2019.” That same zip archive also contains a “README” text file with more information about the test cases. Implementers should review their organizational priorities and develop a similar testing framework and test cases prior to implementation in a production environment.

Testing the CQL itself is just one of the many levels of testing required prior to deployment of a CDS artifact. As discussed in Section 10, integration of CQL into an EHR requires both a capability to execute CQL CDS artifacts, as well as ensuring the required data inputs are mapped from their local formats into what is expected by the CQL. A set of integration tests which parallel the test cases referenced above should be considered a necessary step prior to live deployment of the CQL. For the Anthrax CDS project, this step has been replaced with a synthetic pilot, which is described in the Anthrax CDS Validation Report [21].

7. Implementation Checklist

Boxwala, et al. [22] developed a framework for representing clinical guideline recommendations in a structured way as they are transformed into CDS artifacts. The four “levels” of knowledge representation are [23]:

1. **Narrative** text created by a guideline or quality measure developer.
2. **Semi-structured** text that organizes and describes the recommendations in preparation for CDS implementation.
3. **Structured** code that is interpretable by a computer, including data elements, value sets, and decision support logic.
4. **Executable** code that is interpretable by a computer and integrated into an EHR at the local level. This level will typically vary from site to site due to local factors.

The Anthrax CDS artifact is a Level 3 or so-called structured CDS artifact because it consists of executable code written in CQL but has not been integrated into an EHR. This is depicted in Figure 3 below.



3. Structured code that is interpretable by a computer (includes data elements, value sets, logic).

Figure 3. Knowledge Level of Anthrax Post-Exposure Prophylaxis Clinical Decision Support Artifact
(image source: <https://cds.ahrq.gov/cdsconnect/about>)

Since the Anthrax PEP CDS artifact is not a Level 4 artifact, potential implementers must be aware of the activities that must be undertaken to integrate this CDS artifact into their EHR as part of a local implementation. Specific aspects of integration are discussed in Section 10; the remainder of this section addresses the initial steps potential implementers should take while considering this CDS artifact.

Before attempting to integrate this CDS artifact into a production setting, potential implementers should consider the following recommended actions:

- ✓ Review this implementation guide, paying close attention to Sections 3, 4, and Appendix A (the decision log).
- ✓ Review the CDS artifact metadata and semi-structured (Level 2) representation of the CDS artifact, which should accompany this implementation guide.
- ✓ Ensure that your organization understands and agrees with the intended goals of the clinical guidelines upon which this CDS artifact is based.
- ✓ Review the CQL logic files, paying close attention to the Assumptions section and noting what resources, codes, and value sets are required.
- ✓ Identify any resources, codes, and value sets that are not locally available, and assess the level of effort required to provide mapped equivalents.
- ✓ Identify a mechanism for executing CQL within your EHR; options are discussed in Section 10.

- ✓ Review the supporting documentation (Section 5.2) to understand the format of the CDS artifact outputs.
- ✓ Review the automated test files (Section 6), which provide examples of synthetic patient records which the CDS artifact should be able to process.
- ✓ Implement a local testing capability that mirrors the process described in Section 6.
- ✓ Prepare documentation and training material for clinical staff. The materials should include an overview of this CDS artifact, modifications made as part of the local implementation, directions for interacting with the CDS artifact, and contact information for local assistance if functionality does not line up with expectations.

8. Potential Reuse Scenarios

As described in Section 5.1, the Anthrax PEP CDS artifact already reuses three existing CQL libraries. One of these libraries was augmented to support FHIR STU3 and FHIR R4 data models; these changes are noted in one of the text files accompanying the CQL and could be made available to other efforts.

The Anthrax PEP CQL provides examples for processing as well as generating FHIR resources within the code. These examples can be used to provide a starting point for other CDS artifacts needing to work with FHIR resources. The types used by the Anthrax CQL include the FHIR DSTU2 [15], FHIR STU3 [16], and FHIR R4 [17] resources listed in Figure 4 below. Note that each version of the Anthrax PEP CQL assumes a different FHIR data model, which is also used for the generated FHIR resources.

CQL library name	Anthrax_PEP_Adults_FHIRv102	Anthrax_PEP_Adults_FHIRv300	Anthrax_PEP_Adults_FHIRv400			
CQL data model (FHIR)	DSTU2	STU3	R4			
FHIR resources generated by CQL						
Device	DSTU2	STU3	R4			
Flag	DSTU2	STU3	R4			
DetectedIssue	DSTU2	STU3	R4			
<u>MedicationRequest</u>	STU3	STU3	R4			
<u>ImmunizationRecommendation</u>	STU3	STU3	R4			
<u>ActivityDefinition</u>	STU3	CPG-On-FHIR	STU3	CPG-On-FHIR	R4	CPG-On-FHIR **
<u>PlanDefinition</u>	STU3	CPG-On-FHIR	STU3	CPG-On-FHIR	R4	CPG-On-FHIR **
Library *	STU3	CPG-On-FHIR	STU3	CPG-On-FHIR	R4	CPG-On-FHIR **

CPG-On-FHIR: Indicates resources align with profiles posted at: <http://build.fhir.org/ig/HL7/cqf-recommendations/profiles.html>

* Library resource actually contains the CQL in base64 encoded format.

** CPG-On-FHIR profiles currently aligned to STU3. The R4 implementation makes a best-effort attempt to align to profiles given changes to the resources in FHIR R4.

Figure 4. Table showing types and versions of the FHIR resources generated by the CDS artifact.

9. General Information about Clinical Quality Language

The CQL has been designed to represent clinical knowledge so that it can be applied in both the CDS and Clinical Quality Measures domains [1]. It allows the creation of so-called knowledge CDS artifacts for encoding clinical quality and decision concepts. A powerful aspect of CQL is its close integration with the FHIR standard for representing and communicating healthcare information resources. FHIR provides a data model upon which CQL is able to interact with patient records. Technical aspects related to executing CQL code are given in Section 10.

10. Integration with the Electronic Health Record

Section 7 provided an initial checklist that potential implementers of this CDS artifact should consider prior to integration with a production EHR environment. This section provides some guidance with respect to some of the more technical aspects, including CQL execution and resource mapping.

10.1 Clinical Quality Language Execution

CQL code is meant to be human-readable and is not directly executable by computers. It must first be converted to machine-processable format called the ELM [24]. The CQL specification cites a reference implementation of a CQL-to-ELM translator written in the Java programming language; it is available online [25] under an Apache 2.0 license. Converting CQL to ELM is not only the first step towards EHR integration of the CDS artifact, but it also provides a mechanism for checking the CQL for syntax errors (i.e., that the CQL adheres to the language specification).

Potential integrators should ensure that they can correctly convert the provided CQL to ELM in their development environment. It should be noted that this is not a necessary step, since a copy of the ELM is provided with this CDS artifact. Potential integrators can simply proceed with these instructions using the supplied ELM representation. However, being able to produce an ELM representation that matches the supplied copy can serve as a good consistency check on the CDS artifact.

Once the ELM representation of a CDS artifact has been created, additional software is needed to execute the converted expressions against a patient health record. A reference implementation written in CoffeeScript is available online [26]. This reference implementation assumes that patient records are provided in a custom format. To facilitate integration with FHIR, an additional library is provided for exposing FHIR patient bundles [27] to the CQL execution framework [28]. Both sets of software are freely available under an Apache 2.0 license.

A final aspect of CQL execution relates to providing the CDS artifact with the data it needs to determine the correct recommended care plan. The CDS artifact performs several queries against a patient's health record, whereby certain FHIR resources (see Section 8) are searched, retrieved, and filtered according to the CDS artifact logic. As part of the local EHR integration, a mechanism must be put in place to ensure that the necessary patient information¹ is made available to the CDS artifact as a FHIR bundle. How this is accomplished depends upon the local EHR and is discussed further in the next section.

10.2 Resource Mapping

The Anthrax CDS artifact makes certain assumptions regarding how information about the patient is stored in the EHR. Specifically:

¹ The types of patient information used by the CDS are described in the "data_requirements" PDF file (see **Error! Reference source not found.**).

- Anthrax exposure represented by one of two codes in either a Condition or Observation FHIR resource. The parameter `Exposure_Look_Back_Period` controls how far back to filter potential exposure resources. Default is 60 days.
- Asymptomatic represented by SNOMED-CT code 84387000 in an Observation FHIR resource. Asymptomatic Observation must occur on the same day or after the exposure date.
- Existing antimicrobial Rx are found by querying MedicationStatement FHIR resources, as well as MedicationOrder (for the DSTU2 version) or MedicationRequest (for the STU3 and R4 versions).
- Administration of the anthrax vaccine represented by one of the sequential SNOMED-CT procedure codes. This is how past doses are discovered via querying for Procedure FHIR resources.
- The recommended spacing between subsequent doses of the vaccine is controlled by the parameter `Spacing_Between_Vaccine_Doses`, which has a default value of two weeks (i.e., 14 days). A patient undergoing anthrax PEP will be recommended their next vaccine dose only if two weeks have elapsed since their last administered dose and if they have not received the recommended allotment of three doses.
- Pregnancy can be represented as an Observation or a Condition FHIR resource. Both types of resources are examined to determine if the patient is pregnant.
- Allergies and intolerances are discovered by querying for AllergyIntolerance FHIR resources that contain ingredient/substance codes for any of the potentially recommended PEP treatments. This includes the antimicrobials, the vaccine, and latex.
- Alerts are communicated via either DetectedIssue or Flag FHIR resources.
- Aside from the alerts, the main output of this CDS artifact is an order set. It is represented via FHIR ActivityDefinition and PlanDefinition resources. Since these resources are not available in FHIR DSTU2, that version of the Anthrax PEP CQL assumes FHIR R3 for these outputs. When FHIR R3 is used for ActivityDefinition and PlanDefinition resources, they will conform to the draft profiles available as part of the CDC Adapting Clinical Guidelines for the Digital Age Implementation Guide [29].
- A Library resource is available for all three versions of the Anthrax PEP CQL, which describes in detail the data requirements of the artifact. When FHIR R3 is used for the outputs, the Library resource conforms to the aforementioned profile [29].
- This CDS artifact outputs various FHIR resource objects. For the purposes of local FHIR references, it is assumed all generated FHIR resources will be returned in a single FHIR bundle.

If at the local level certain required information is captured in a way which is inconsistent with any of the above, that local information must be *mapped* to resources that are consistent with the CDS artifact logic. Ensuring that all the required resources are properly mapped can be one of the most time-consuming integration activities. Having a robust internal testing mechanism setup (see Section 6) can greatly increase the chances of a successful integration.

Appendix A. Decision Log

A.1 Clinical Decision Support Artifact Semi-Structured Logic

Table 2 below provides the semi-structured logic statements for the inclusion and exclusion criteria, and Table 3 includes the semi-structured logic for patient-specific data that populates the anthrax CDS artifact to serve as a reference for decision log entries.

Table 2. Semi-structured Inclusion and Exclusion Logic

Inclusions and Exclusions
Inclusions
Part #1: Individuals ≥ 18 years old with documented exposure to anthrax within the past 60 days, without a diagnosis of anthrax, and may be symptomatic Part #2: Individuals ≥ 18 years old with documented exposure to anthrax within the past 60 days, without a diagnosis of anthrax, and who are asymptomatic
Exclusions
Part #1: Individuals < 18 years old, with no documented exposure to anthrax, exposure greater than 60 days prior, a diagnosis of anthrax, or who are asymptomatic Part #2: Individuals < 18 years old, with no documented exposure to anthrax, exposure greater than 60 days prior, a diagnosis of anthrax, or who are symptomatic

Table 3. Semi-structured Clinical Decision Support Intervention Logic

CDS Intervention
1. If patient is greater than or equal to 18 years of age, they have been exposed to Anthrax within the past 60 days, and if they do not have a diagnosis of anthrax. (# of days between date of exposure and current date)
Intervention: Post Alert: “If patient has signs or symptoms consistent with anthrax, conduct a full diagnostic evaluation for anthrax. Signs and symptoms of anthrax include fever, chills, headache, malaise, nausea, vomiting, diarrhea, abdominal pain, diaphoresis, anorexia, nonproductive cough, difficulty breathing, dyspnea, stridor, hypoxemia, hypotension, shock, cyanosis, chest pain, lymphadenopathy, cutaneous ulcer, and black eschar. If patient has NO signs or symptoms consistent with anthrax, document ‘asymptomatic SNOMEDCT 84387000.’”
2. If patient is greater than or equal to 18 years of age, they have been exposed to Anthrax within the past 60 days, they do not have a diagnosis of anthrax (# of days between date of exposure and current date), and if asymptomatic
(2.A.) If patient has an existing prescription for ciprofloxacin, doxycycline, levofloxacin, moxifloxacin, or clindamycin
Intervention:

CDS Intervention

IF ciprofloxacin, DISPLAY “The patient has an active prescription for ciprofloxacin. Evaluate the dosage and duration to ensure a 60-day regimen of appropriate antibiotic post-anthrax exposure: Ciprofloxacin 500 mg by mouth every 12 hours for 60 days.”

IF doxycycline, DISPLAY “The patient has an active prescription for doxycycline. Evaluate the dosage and duration to ensure a 60-day regimen of appropriate antibiotic post-anthrax exposure: Doxycycline 100 mg by mouth every 12 hours for 60 days.”

IF levofloxacin, DISPLAY “The patient has an active prescription for levofloxacin. Evaluate the dosage and duration to ensure a 60-day regimen of appropriate antibiotic post-anthrax exposure: Levofloxacin, 750 mg by mouth once daily for 60 days.”

IF moxifloxacin, DISPLAY “The patient has an active prescription for Moxifloxacin. Evaluate the dosage and duration to ensure a 60-day regimen of appropriate antibiotic post-anthrax exposure: ‘Moxifloxacin 400 mg by mouth once daily for 60 days.’”

IF clindamycin, DISPLAY “The patient has an active prescription for clindamycin. Evaluate the dosage and duration to ensure a 60-day regimen of appropriate antibiotic post-anthrax exposure: Clindamycin 600 mg by mouth every 8 hours for 60 days.”

(2.B.) If patient is pregnant**Intervention:**

IS patient allergic to ciprofloxacin or doxycycline.

IF YES, DISPLAY “ Potential patient allergy to ciprofloxacin. Confirm allergy status.”

AND/OR “ Potential patient allergy to doxycycline. Confirm allergy status.”

AND DISPLAY “Options for treatment, depending on allergies, include first choice (309309) ciprofloxacin 500 mg by mouth every 12 hours for 60 days with full glass of water. Provide patient education on medications.

CONTRAINDICATIONS: Diagnosis of myasthenia gravis and taking tizanidine (Zanaflex).

CAUTIONS: If patient is taking blood thinners, oral antidiabetic drugs, seizure drugs, theophylline, drugs that prolong QT interval, duloxetine (Cymbalta), zolpidem (Ambien), clozapine, or any other drug that may interact and cause serious side effects, consider another antibiotic regimen.

ADDITIONAL INSTRUCTIONS: Pregnant women at risk for inhalation anthrax should receive antimicrobial drug therapy regardless of pregnancy trimester

OR “Options for treatment, depending on allergies, include second choice(1650143) doxycycline 100 mg by mouth every 12 hours for 60 days with full glass of water. Provide patient education on medications.

CAUTION: If patient is taking blood thinners, seizure drugs, or any other drug that may interact and cause serious side effects, consider another antibiotic regimen.

ADDITIONAL INSTRUCTIONS: Pregnant women at risk for inhalation anthrax should receive antimicrobial drug therapy regardless of pregnancy trimester.”

OR “Options for treatment, depending on allergies, include second choice(1650143) doxycycline 100 mg by mouth every 12 hours for 60 days with full glass of water. Provide patient education on medications.

CAUTIONS: If patient is taking blood thinners, seizure drugs, or any other drug that may interact and cause serious side effects, consider another antibiotic regimen.

CDS Intervention

ADDITIONAL INSTRUCTIONS: Pregnant women at risk for inhalation anthrax should receive antimicrobial drug therapy regardless of pregnancy trimester.”

(2.C.) If patient is not pregnant**Intervention:**

IS patient allergic to ciprofloxacin or doxycycline?

IF YES DISPLAY “ Potential patient allergy to ciprofloxacin. Confirm allergy status.”

AND/OR “ Potential patient allergy to doxycycline. Confirm allergy status.”

AND DISPLAY “Options for treatment, depending on allergies, include (309309) ciprofloxacin 500 mg by mouth every 12 hours for 60 days with full glass of water. Provide patient education on medications.

CONTRAINDICATIONS: Diagnosis of myasthenia gravis and taking tizanidine (Zanaflex).

CAUTIONS: If patient is taking blood thinners, oral antidiabetic drugs, seizure drugs, theophylline, drugs that prolong QT interval, duloxetine (Cymbalta), zolpidem (Ambien), clozapine, or any other drug that may interact and cause serious side effects, consider another antibiotic regimen.”

OR “Options for treatment, depending on allergies, include (1650143) doxycycline 100 mg by mouth every 12 hours for 60 days with full glass of water. Provide patient education on medications.

CAUTION: If patient is taking blood thinners, seizure drugs, or any other drug that may interact and cause serious side effects, consider another antibiotic regimen.”

(2.D.) For all patients**Intervention:**

IS patient allergic to levofloxacin OR moxifloxacin OR clindamycin?

IF YES, DISPLAY “Potential patient allergy to levofloxacin. Confirm allergy status.”

AND/OR “Potential patient allergy to moxifloxacin. Confirm allergy status.”

AND/OR “Potential patient allergy to clindamycin. Confirm allergy status.”

AND DISPLAY “If patient allergic to ciprofloxacin or doxycycline, second-line antibiotics include the following options, depending on allergies: ‘Levofloxacin 750 mg by mouth once daily for 60 days.’

ADDITIONAL INSTRUCTIONS: Pregnant women at risk for inhalation anthrax should receive antimicrobial drug therapy regardless of pregnancy trimester.”

OR ‘Moxifloxacin 400 mg by mouth once daily for 60 days.’

ADDITIONAL INSTRUCTIONS: ‘Pregnant women at risk for inhalation anthrax should receive antimicrobial drug therapy regardless of pregnancy trimester.’

OR ‘Clindamycin 600 mg by mouth every 8 hours for 60 days.’

ADDITIONAL INSTRUCTIONS: ‘Pregnant women at risk for inhalation anthrax should receive antimicrobial drug therapy regardless of pregnancy trimester.’”

AND IF YES TO ALL – “Consider allergies and alternative antibiotic regimens.”

(2.E.) For all patients**Intervention:**

IS patient allergic to BioThrax (anthrax vaccine antigen or ingredient)?

CDS Intervention	
IF YES, DISPLAY “Potential patient allergy to BioThrax. Assess for BioThrax vaccine allergy. Epinephrine solution (1:1000) should be available for immediate use in the event that an anaphylactic reaction occurs.”	
(2.F.) For all patients	
Intervention:	
IS patient allergic to latex?	
IF YES, DISPLAY “Patient has a history of latex allergy. The stopper of the BioThrax vial contains latex. Confirm allergy status. Epinephrine solution (1:1000) should be available for immediate use in the event that an anaphylactic reaction occurs.”	
(2.G.) For all patients,	
(2.G.1) IF an anthrax vaccination date is missing	
OR IF there is a missing or non-sequential anthrax vaccination	
Intervention: Display “Potential BioThrax vaccine series problem(s) identified. A vaccine in the recommended series might be missing or a vaccination date might be missing. Review BioThrax (anthrax) vaccine series history.”	
(2.G.2) IF Third anthrax vaccination OR fourth anthrax vaccination is documented	
Intervention: Stop	
(2.G.3) IF Second anthrax vaccination is documented AND procedure date minus current date is > 14 days	
Intervention: DISPLAY “Administer BioThrax 0.5 mL subcutaneous and document third anthrax vaccination.”	
(2.G.4) IF First anthrax vaccination is documented AND procedure date minus current date is > 14 days	
Intervention: DISPLAY “Administer BioThrax 0.5 mL subcutaneous and document second anthrax vaccination.”	
(2.G.5) IF not	
Intervention: DISPLAY “Administer BioThrax 0.5 mL subcutaneous and document first anthrax vaccination.”	

A.2 Concept Definitions from the Semi-Structured Logic

Table 4 defines many of the terms used in the semi-structured representation of the CDS artifact logic to ensure clarity and provide awareness of how and why each data element was defined as it was.

Table 4. Semi-structured Logic Concept Definitions

Location in CDS Logic	Concept	Definition and/or Rationale
Inclusions	“documented exposure”	A code for anthrax exposure is present in the patient’s record.

Location in CDS Logic	Concept	Definition and/or Rationale
Inclusions	“within the past 60 days”	The current date minus the date of the most recent anthrax exposure is less than or equal to 60 calendar days.
Inclusions	“without a diagnosis of anthrax”	There is not a diagnostic code for any form of anthrax in the patient’s record.
Inclusions	“may be symptomatic”	Potentially having signs and symptoms consistent with anthrax.
Inclusions	“asymptomatic”	A documented code in the patients record of “asymptomatic”; for example, SNOMED-CT 84387000.
Inclusions	“exposed to anthrax”	A code for anthrax exposure is present in the patient’s record.
Interventions	“If patient has signs or symptoms consistent with anthrax”	Signs and symptoms most commonly associated with inhalation, gastrointestinal, and cutaneous anthrax. Examples provided in the CDS artifact include fever, chills, headache, malaise, nausea, vomiting, diarrhea, abdominal pain, diaphoresis, anorexia, nonproductive cough, difficulty breathing, dyspnea, stridor, hypoxemia, hypotension, shock, cyanosis, chest pain, lymphadenopathy, cutaneous ulcer, and black eschar.
Interventions	“...no signs of symptoms consistent with anthrax document asymptomatic...”	Indicate a code such as SNOMEDCT 84387000 to indicate the patient is without signs or symptoms at that time.
Interventions	“conduct a full diagnostic evaluation for anthrax”	Diagnostic workup includes a variety of components (e.g., laboratory tests, electrocardiogram, radiographs) as appropriate. The Centers for Disease Control and Prevention Expert Panel Meetings on Prevention and Treatment of Anthrax in Adults: Technical Report, Table 1 provides a detailed list for consideration [6].
Interventions	“If patient has an existing prescription for”	There is a current active prescription documented in the patient’s record.
Interventions	“ciprofloxacin, doxycycline, levofloxacin, moxifloxacin , or clindamycin”	The value sets corresponding to these medications are for oral or injectable forms, not creams, lotions, foams, suppositories, gels, medicated pads, or soaps.

Location in CDS Logic	Concept	Definition and/or Rationale
Interventions	“The patient has an active prescription...”	There is a prescription in the patient’s record that includes the current time frame.
Interventions	“...for ciprofloxacin. Evaluate the dosage and duration to ensure a 60-day regimen of appropriate antibiotic post-anthrax exposure: Ciprofloxacin 500 mg by mouth every 12 hours for 60 days”	The dosage and frequency of ciprofloxacin, 500 mg by mouth every 12 hours, must be prescribed for a total of 60 calendar days. If this criterion is not met, the patient requires a new prescription for an antimicrobial to meet the recommendation for PEP. This logic also applies to doxycycline, levofloxacin, moxifloxacin, and clindamycin.
Interventions	“pregnant”	Abdominal and normal pregnancy as well as tubal, ectopic pregnancy, and other diagnoses that could indicate a patient is pregnant. There is a documented findings disorder or diagnostic code meeting this criterion in the patient’s record.
Interventions	“options for treatment, depending on allergies...”	Options per the guidelines used for this CDS artifact (reference bibliography). Allergies should be evaluated for type and severity prior to excluding a medication for use.
Interventions	“first choice”	Best option for pregnant patients.
Interventions	“second choice”	Second-best option for pregnant patients.
Interventions	“appropriate”	According to the CDC guidelines for the dosage, frequency, and duration of administration of antimicrobial medications.
Interventions	“allergic”	A damaging immune response by the body to a substance to which it becomes hypersensitive, includes all negative reactions (e.g., topical, respiratory, minor, severe).
Interventions	“Potential patient allergy to ciprofloxacin”	An allergy code for the medication substance is in the patient’s record. This logic also applies to statements indicating allergies to the other medications.
Interventions	“Confirm allergy status”	Verbal confirmation from the patient about presence or absence of allergies related to each medication and the anthrax vaccine.

Location in CDS Logic	Concept	Definition and/or Rationale
Interventions	“at risk for inhalation anthrax”	Persons who have a documented exposure to anthrax within the past 60 days.
Interventions	“contraindications”	Specific situation in which a drug, procedure, or surgery should not be used because it may be harmful to the person.
Interventions	“cautions”	Issues that should be addressed by the provider prior to proceeding further with the CDS or clinical care.
Interventions	“additional instructions”	Additional key pertinent information for the patient.
Interventions	“Provide patient education on medications.”	Provide materials to the patient to reference including precautions related to long-term medication usage for anthrax PEP.
Interventions	“alternative antibiotic regimens”	Antimicrobial medications other than the first- or second-line medications as provided in the CDC anthrax guidelines that may be effective.
Interventions	>14 days	The current date minus the date of the last BioThrax (anthrax) vaccine is greater than 14 calendar days.
Interventions	“administer BioThrax...and document first (second, third) anthrax vaccine”	Administer the anthrax vaccine and document which vaccine in the series the administration represents.

A.3 Clinical Decision Support Artifact Development Decision Log

Numerous decisions were made by the CDS Artifact Development Team while translating the CDC clinical practice guidelines and developing the structured representation of this CDS artifact. Table 5 provides insight on those decisions.

Table 5. Structured Artifact Decision Log

Decision Category	Concept	Rationale
Add explanation	Use of general SNOMED-CT exposure code to anthrax versus a code specific for inhalation anthrax	Although this CDS artifact is for inhalation anthrax, a general exposure code to anthrax is used to trigger the event to provide screening to persons exposed to anthrax to exclude persons with any signs or symptoms consistent with anthrax disease.
Add explanation	Inclusion of adults ≥ 18 without an upper age limit	The anthrax vaccine guideline [9] specifies an upper age limit of 65 years in the PEP protocol. However, the more recent guidelines addressing PEP in adults [5] [6]

Decision Category	Concept	Rationale
		did not include an upper age limit. The authors verified with CDC anthrax SMEs from the Bacterial Special Pathogens Branch, Division of High-Consequence Pathogens & Pathology, CDC, that there should not be an upper age limit (2018, personal communication). Children and adolescents under the age of 18 are not included in this CDS artifact.
Add explanation; verify completeness	CDS contains two parts	Anyone exposed to anthrax within the past 60 days must be assessed for anthrax disease. Thus, this CDS artifact includes those exposed but without a confirmed diagnosis of anthrax. The first part screens for persons with signs and symptoms consistent with anthrax and recommends a full diagnostic evaluation. The second part focuses on those persons who are asymptomatic and provides post-exposure prophylaxis.
Add explanation	Time limit of 60 days since exposure	The exposure time limit of 60 days is from the CDC anthrax guidelines. Antimicrobial agents are effective against germinating and vegetative <i>B. anthracis</i> , but dormant spores are refractory to antimicrobials. Inhalation anthrax has developed up to 58 days after experimental aerosol exposure in primates that received post-exposure antimicrobial prophylaxis for the first 30 days after aerosol exposure [9]. Reported incubation periods for inhalation anthrax in humans range from 1–43 days [9].
Verify completeness	If presenting with signs and symptoms, “conduct full diagnostic workup,” CDS stops	If the patient has signs and symptoms of anthrax, before proceeding the patient requires a full diagnostic workup such as the one provided in the Centers for Disease Control and Prevention Expert Panel Meetings on Prevention and Treatment of Anthrax in Adults [5] [6], which is outside of scope for this CDS artifact.
Add explanation	Signs and symptoms listed in CDS artifact	The signs and symptoms listed are found in the PHVS_SignsSymptoms_Anthrax value set [27], CDC anthrax guidelines in the reference list, and approved by CDC anthrax SMEs (2018, personal communication). The signs and symptoms are those most commonly related to inhalation, gastrointestinal, and cutaneous anthrax and are not an exhaustive list.
Add explanaton	Value sets	The authors searched value sets in PHIN VADS and on the Value Set Authroity Center (VSAC) for ones pertaining to signs and symptoms of anthrax, pregnancy, the antimicrobial medications, and allergies. Parts of the PHIN VADS signs and

Decision Category	Concept	Rationale
		symptoms value set was inserted as text; and one value set from VSAC on pregnancy was used. There were no applicable value sets for the medications or allergies. The authors developed value sets if at least two codes were included and published them on VSAC
Add explanation	Defining “if tolerated” as “allergies.”	The guidelines did not offer any definitive guidance on what “if tolerated” represents. The authors chose to represent “not tolerated” as allergies and intolerances that could be represented using a FHIR DSTU2 AllergyIntolerance resource. “If tolerated” is the absence of any AllergyIntolerance resource in the patient record. If there is an indication that the patient cannot tolerate a particular recommended treatment, an alert message “confirm allergy status” is provided as a reminder to the clinician to ask about reactions related to the medication. This CDS does not specifically address what constitutes non-allergy intolerances.
Add explanation	Use of RxNorm substance codes to determine allergies for doxycycline, ciprofloxacin, levofloxacin, clindamycin, and moxifloxacin	The documentation of allergies varies across EHR systems. RxNorm codes are the accepted standard [12]. Using the overarching ingredient code captures the antimicrobial formulations available for prescription.
Add explanation	Use of SNOMED-CT substance codes to determine allergies to latex	Latex is not a medication, and therefore RxNorm codes could not be used. SNOMED-CT substance codes are used to capture documented allergies and intolerances via an AllergyIntolerance FHIR resource; see Section 10.2.
Add explanation	Use of the BioThrax (anthrax) vaccine code to determine allergies	There is not a specific code for BioThrax (anthrax vaccine) related allergies. Thus, the CVX vaccine code is used and addressed as an AllergyIntolerance FHIR resource; see Section 10.2.
Verify completeness	“confirm allergy status”	The provider should evaluate all allergies to determine the severity of the reaction as well as to determine if the patient has an allergy not captured by the CDS or EHR.
Add explanation	Options for treatment presented even if the patient is allergic	The most effective first-line antimicrobials for anthrax PEP must be considered even if the patient has a history of an associated allergy. Based on the type and severity of the allergic reaction, the antimicrobial might not be absolutely contraindicated.

Decision Category	Concept	Rationale
Add explanation	Antimicrobial drug therapy suggested in the CDS artifact	The approach to prevention and treatment of anthrax differs from that for other bacterial infections. The production of toxin, potential for antimicrobial drug resistance, frequent occurrence of meningitis, and presence of latent spores must be taken into account when selecting PEP or a combination of antimicrobial drugs for treatment of anthrax [5] [6]. The antimicrobials in the CDS are recommended in the CDC anthrax guidelines.
Add explanation	Amoxicillin for pregnant women	The anthrax vaccine guideline specifies amoxicillin as a first-line medication for pregnant women. However, the authors chose to use a more recent guideline, specific to pregnancy and postpartum women, which includes only ciprofloxacin and doxycycline as first-line antimicrobials for PEP [8].
Add explanation	“first choice” “second choice”	In pregnancy, ciprofloxacin (first choice) is preferred over doxycycline (second choice) in preventing anthrax per the Special Considerations for Prophylaxis for and Treatment of Anthrax in Pregnant and Postpartum Women (2014) [8].
Add explanation	Additional instruction of “Pregnant women at risk for inhalation anthrax should receive antimicrobial drug therapy regardless of pregnancy trimester.”	Anthrax is associated with maternal and fetal deaths. Given the severity of anthrax, pregnant, post-partum, and lactating women should receive anthrax PEP the same as nonpregnant adults unless there are compelling reasons for these recommendations to differ. However, the risks and benefits should be discussed with the mother [8].
Identify origin	“contraindications”	Those included are specifically identified in the proposed “Example Mass Screening Algorithm for Stockpiled Oral Antibiotics for Anthrax Post-Exposure Prophylaxis” [30].
Identify origin	“cautions”	Those included are specifically identified in the proposed “Example Mass Screening Algorithm for Stockpiled Oral Antibiotics for Anthrax Post-Exposure Prophylaxis” [30].
Add explanation	Contraindications and cautions are listed for ciprofloxacin and doxycycline but not	Guidelines outlining clinical situations which are contraindications and cautions for using the first-line antimicrobials, ciprofloxacin and doxycycline, for anthrax PEP are available [3] [4]. Published CDC guidance for contraindications and cautions for the

Decision Category	Concept	Rationale
	for levofloxacin, moxifloxacin, or clindamycin	second-line antimicrobials was not available to develop this CDS.
Add explanation	“Provide patient education on medications.”	Since ciprofloxacin and doxycycline are the first-line antimicrobial medications, CDC recommends providing materials on long-term use. The Ciprofloxacin and Doxycycline guidelines for Post-Exposure Prophylaxis of Anthrax: Emergency Use Instructions for Healthcare Providers” have information for providers that could potentially be used to develop patient education materials [3] [4].
Add Explanation	Use of specific anthrax immunization codes indicating sequence number to identify previous immunizations for anthrax	It is important to identify specifically which anthrax vaccine(s) in the sequence the patient has previously been administered and currently requires. The CDS is based only on SNOMED procedure codes for vaccine administration. Codes included in the CDS represent the sequential number of BioThrax (anthrax) vaccines from one to five. For PEP, three anthrax vaccinations are a full series. The codes for vaccines four and five are included because persons might have been previously immunized with a five-vaccine series for pre-exposure prophylaxis (e.g., members of the U.S. military).
Add explanation	Sequence of anthrax vaccines	Each of the three vaccines is administered at least 14 days. Persons fully vaccinated for anthrax prior to exposure might require a booster vaccine, which is not included in this CDS artifact.

Acronyms

CDC	Centers for Disease Control and Prevention
CDS	Clinical Decision Support
CQL	Clinical Quality Language
DSTU	Draft Standard for Trial Use
EHR	Electronic Health Record
EKG	Electrocardiogram
ELM	Expression Logical Model
FDA	Food and Drug Administration
FHIR	Fast Healthcare Interoperability Resources
GI	Gastrointestinal
GRADE	Grading of recommendations, assessment, development, and evaluation
HL7	Health Level 7
PDF	Portable Document Format
PEP	Post-Exposure Prophylaxis
PHIN VADS	Public Health Information Network Vocabulary Access and Distribution System
SME	Subject Matter Expert
SNOMED	Systematized Nomenclature of Medicine
SNOMED-CT	Systematized Nomenclature of Medicine – Clinical Terms
STU	Standard for Trial Use
TDD	Test Driven Development
VSAC	Value Set Authority Center
YAML	YAML Ain't Markup Language

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