Antibiotic Interpretation Algorithms and Resources

# Introduction

This document outlines the interpretation algorithms, as well as providing information about the structure and intent of each resource table’s key columns. The tables are intended to externalize the information required interpret quantitative antibiotic test results. They are provided in a simple text-file format, which is easily consumed by 3rd-party software. It also facilitates periodic updates as the guidelines change without requiring a change to the business logic of those applications.

In addition to the resource tables, the appendix contains SQL queries which demonstrate some of the steps described below. The resource files could be imported to a database of your choice, then explored through an adaptation of the SQL below (which is for SQLite) into your chosen dialect.

# Interpretation algorithm – single measurement

This algorithm describes how to interpret a single test measurement on its own by applying the applicable intrinsic resistance and breakpoint rules contained in the resource tables. This algorithm is part of the full algorithm for generating an interpretation for a complete isolate, which also depends upon the expert interpretation rules.

1. Determine whether the organism and antibiotic combination in question has a matching rule in the Intrinsic Resistance table. This will also involve the Organisms table to extract information about the organism (such as the genus for intrinsic rules which apply to a whole genus).
   1. If yes, then this organism is intrinsically resistant to the antibiotic, and should be interpreted as resistant.
2. If the organism is not intrinsically resistant (an absence of matching intrinsic resistance rules above), then we determine if there are applicable breakpoints. After filtering the Breakpoints table on your desired guideline and year, the Organisms table is used to further match the Breakpoints table with your organism. For example, a breakpoint rule might apply to the GENUS\_CODE “HA-“, so we must use the Organisms table to determine this membership based on the actual organism code, which might be “hin” for *Haemophilus influenzae*.
   1. If one or more breakpoint rules match the organism and antibiotic, you can either evaluate and report all of them, or sort them in a particular order to determine the “default” or “best” interpretation.
   2. The precise order of breakpoints partially depends upon your needs. For example, a veterinary isolate might require that the BREAKPOINT\_TYPE = “Animal” take precedence over any “Human” breakpoints.
   3. There are also non-variable parts to the sorting order. For example, we must prefer a more-specific breakpoint over a less-specific, such as favoring a breakpoint specifically for E. coli over a broader breakpoint which applies for all Enterobacteriaceae.
3. Now that you have a sorted list of breakpoints, you can evaluate one or more of them to determine the interpretation for your measurement.

# Interpretation algorithm – complete isolate

Prior to evaluating any intrinsic resistance or breakpoints, we must apply the expert rules when interpreting a complete isolate because the interpretation of one antibiotic measurement or data field might impact the interpretations of several other antibiotics if an expert interpretation rule is activated. This algorithm would be applied separately for each isolate in a data file.

1. Determine if any of the expert interpretation rules apply to the isolate. For a rule to apply, it must match both on the organism (requiring a join to the Organisms table as above), as well as having satisfied the RULE\_CRITERIA.
   1. RULE\_CRITERIA are of three types.
      1. A three-letter antibiotic code. e.g., OXA=NS, which means “Not susceptible to Oxacillin”
      2. A data field. e.g., ESBL=+, which means “The ESBL data field must have a value of ‘+’”
      3. Antibiotic class. There is only one example in use presently: CEPH3=R, meaning “Resistant to any of the Cephalosporin III antibiotics.” In this case, it will be necessary to join or otherwise lookup the PROF\_CLASS=CEPH3 antibiotics.
   2. To evaluate RULE\_CRITERIA involving an antibiotic, apply the “single measurement” algorithm for every requisite antibiotic (this means applying the breakpoints, since there wouldn’t be an expert rule involving intrinsic resistance).
2. For each activated expert interpretation rule, the associated AFFECTED\_ANTIBIOTICS for that rule may now be interpreted as resistant.
   1. AFFECTED\_ANTIBIOTICS contain two types of values:
      1. A three-letter antibiotic code. e.g., AMC, which means “Amoxicillin/Clavulanic acid”
      2. An antibiotic class name. e.g., Macrolides. This situation requires an additional join or lookup in the Antibiotics table for matches in the CLASS column.
   2. If one of the AFFECTED\_ANTIBIOTICS is contained in your input data, and it has a test measurement for this isolate, this interpretation should be output as resistant.
      1. To prevent later skewing of statistics, you should not report the affected antibiotic as resistant when it does not have a test measurement.
   3. The ANTIBIOTIC\_EXCEPTIONS column contains a list of caveats to the AFFECTED\_ANTIBIOTICS. The expert rule does not apply to the ANTIBIOTIC\_EXCEPTIONS drugs.
3. At this stage, there are 3 sets that the antibiotics measurements and interpretations might fall into.
   1. Measurements interpreted as part of the RULE\_CRITERIA.
      1. For example, if we needed to determine the interpretation of AMC as a precondition for the rule, then the AMC result for the output is known regardless of whether the rule has been activated.
   2. Interpretations which were generated because of the activation of an expert interpretation rule (the AFFECTED\_ANTIBIOTICS).
      1. If an expert rule is activated which affects antibiotic SAM, then the actual measurement for SAM will never be evaluated because the expert interpretation precludes it.
   3. All remaining antibiotic measurements for the isolate.
4. The last stage is to individually apply the “single measurement” algorithm on each of these remaining measurements (items in 3.c) to get their interpretations.

# Appendix

## Data tables

### Antibiotics table – key fields

1. WHONET\_ABX\_CODE
   1. Antibiotic code. This code is used in all other tables which reference specific antibiotic codes.
2. ANTIBIOTIC
   1. Display name for the antibiotic.
3. CLSI, EUCAST, SFM, SRGA, BSAC, DIN, NEO, AFA
   1. Various guideline inclusion fields. Each of these columns will contain an “X” if the associated row is relevant for the guideline.
4. CLASS
   1. This column is needed when an expert interpretation rule mentions a class name as one of the AFFECTED\_ANTIBIOTICS.
5. PROF\_CLASS
   1. This column is only needed in this context to find the CEPH3 drugs relevant for a specific expert interpretation rule.

### Breakpoints table – key fields

1. GUIDELINES
   1. Indicates the guideline which the breakpoint belongs to.
2. YEAR
   1. Indicates the guideline year.
3. TEST\_METHOD
   1. MIC or DISK.
4. ORGANISM\_CODE, ORGANISM\_CODE\_TYPE
   1. The ORGANISM\_CODE\_TYPE indicates which column in the Organisms table ORGANISM\_CODE should match to.
5. BREAKPOINT\_TYPE
   1. Human, Animal, ECOFF
6. HOST
   1. Host species which was infected by the pathogen. Differentiates breakpoints based on the organism hosting the infection. e.g., Human, feline, horse
7. SITE\_OF\_INFECTION
   1. Differentiates breakpoints based on the infection site. e.g., Meningitis versus Non-meningitis.
8. WHONET\_TEST
   1. Encodes the WHONET\_ABX\_CODE, guideline (N for CLSI, E for EUCAST, etc.), as well as the test method (D for disk + potency, M for MIC, E for ETest)
9. R, I, SDD, S
   1. Breakpoint cutoff values.
10. ECV\_ECOFF
    1. ECOFF value when BREAKPOINT\_TYPE = ECOFF.

### Expert interpretation rules table – key fields

1. ORGANISM\_CODE, ORGANISM\_CODE\_TYPE
   1. The ORGANISM\_CODE\_TYPE indicates which column in the Organisms table ORGANISM\_CODE should match to.
2. RULE\_CRITERIA
   1. One or more criteria which must be satisfied to activate the expert interpretation rule.
3. AFFECTED\_ANTIBIOTICS
   1. List of codes indicating sets of antibiotics which should be interpreted as resistant if the rule is activated.
4. ANTIBIOTIC\_EXCEPTIONS
   1. Exceptions to the AFFECTED\_ANTIBIOTICS. The rule applies to all of the AFFECTED\_ANTIBIOTICS, except those on the ANTIBIOTIC\_EXCEPTIONS list.

### Intrinsic resistance table – key fields

1. GUIDELINE
   1. Guideline that this rule belongs to.
2. ORGANISM\_CODE, ORGANISM\_CODE\_TYPE
   1. The ORGANISM\_CODE\_TYPE indicates which column in the Organisms table ORGANISM\_CODE should match to.
3. EXCEPTION\_ORGANISM\_CODE, EXCEPTION\_ORGANISM\_CODE\_TYPE
   1. These columns provide a mechanism for selecting the ORGANISM\_CODE organisms, while excluding the EXCEPTION\_ORGANISM\_CODE set.
4. ABX\_CODE, ABX\_CODE\_TYPE
   1. The ABX\_CODE\_TYPE column indicates which column in the Antibiotics table ABX\_CODE refers to.

### Organisms table – key fields

1. WHONET\_ORG\_CODE
   1. Organism code used by the WHONET software and these resource tables.
2. TAXONOMIC\_STATUS
   1. “C” for current organisms, “O” for outdated terms. Only use the “C” records.
3. ANAEROBE
   1. Indicates whether the organism is an anaerobe.
4. SUBKINGDOM
   1. Indicates whether the organism is Gram-positive or -negative if that is applicable.
5. FAMILY\_CODE, GENUS\_GROUP, GENUS\_CODE, SPECIES\_GROUP, SEROVAR\_GROUP
   1. These fields allow table joins at various levels in the hierarchy.

## SQL queries

### Breakpoints.sql

/\*

This query returns a sorted list of breakpoints for the conditions you define in the WHERE clause.

\*/

SELECT o.ORGANISM, o.WHONET\_ORG\_CODE, b.ORGANISM\_CODE, b.ORGANISM\_CODE\_TYPE, b.GUIDELINES, b.YEAR, b.TEST\_METHOD, b.POTENCY, b.BREAKPOINT\_TYPE, b.HOST, b.SITE\_OF\_INFECTION, b.WHONET\_TEST, b.R, b.I, b.SDD, b.S, b.ECV\_ECOFF

FROM Organisms o

INNER JOIN Breakpoints b

ON b.ORGANISM\_CODE\_TYPE <> 'ALL' AND (

o.SEROVAR\_GROUP IS NOT NULL

AND b.ORGANISM\_CODE\_TYPE = 'SEROVAR\_GROUP'

AND o.SEROVAR\_GROUP = b.ORGANISM\_CODE

) OR (

b.ORGANISM\_CODE\_TYPE = 'WHONET\_ORG\_CODE'

AND o.WHONET\_ORG\_CODE = b.ORGANISM\_CODE

) OR (

o.SPECIES\_GROUP IS NOT NULL

AND b.ORGANISM\_CODE\_TYPE = 'SPECIES\_GROUP'

AND o.SPECIES\_GROUP = b.ORGANISM\_CODE

) OR (

o.GENUS\_CODE IS NOT NULL

AND b.ORGANISM\_CODE\_TYPE = 'GENUS\_CODE'

AND o.GENUS\_CODE = b.ORGANISM\_CODE

) OR (

o.GENUS\_GROUP IS NOT NULL

AND b.ORGANISM\_CODE\_TYPE = 'GENUS\_GROUP'

AND o.GENUS\_GROUP = b.ORGANISM\_CODE

) OR (

o.FAMILY\_CODE IS NOT NULL

AND b.ORGANISM\_CODE\_TYPE = 'FAMILY\_CODE'

AND o.FAMILY\_CODE = b.ORGANISM\_CODE

) OR (

o.ANAEROBE = 'X'

AND b.ORGANISM\_CODE\_TYPE = 'ANAEROBE+SUBKINGDOM\_CODE'

AND ((

o.SUBKINGDOM\_CODE = '+'

AND b.ORGANISM\_CODE = 'AN+'

) OR (

o.SUBKINGDOM\_CODE = '-'

AND b.ORGANISM\_CODE = 'AN-'

))

) OR (

o.ANAEROBE = 'X'

AND b.ORGANISM\_CODE\_TYPE = 'ANAEROBE'

AND b.ORGANISM\_CODE = 'ANA'

)

WHERE o.WHONET\_ORG\_CODE = 'spn'

AND o.TAXONOMIC\_STATUS = 'C'

-- AND b.GUIDELINES = 'EUCAST'

AND b.YEAR = 2021

-- AND b.BREAKPOINT\_TYPE = 'Animal'

-- AND b.TEST\_METHOD = 'MIC'

-- Filter on one drug.

AND b.WHONET\_TEST = 'CRO\_NM'

-- AND b.WHONET\_ABX\_CODE = 'CRO'

ORDER BY o.WHONET\_ORG\_CODE ASC,

b.GUIDELINES ASC,

b.YEAR ASC,

b.TEST\_METHOD ASC,

(

CASE b.BREAKPOINT\_TYPE

WHEN 'Human' THEN 1

WHEN 'Animal' THEN 2

WHEN 'ECOFF' THEN 3

END

) ASC,

b.HOST ASC, (

CASE b.ORGANISM\_CODE\_TYPE

WHEN 'SEROVAR\_GROUP' THEN 1

WHEN 'WHONET\_ORG\_CODE' THEN 2

WHEN 'SPECIES\_GROUP' THEN 3

WHEN 'GENUS\_CODE' THEN 4

WHEN 'GENUS\_GROUP' THEN 5

WHEN 'FAMILY\_CODE' THEN 6

WHEN 'ANAEROBE+SUBKINGDOM\_CODE' THEN 7

WHEN 'ANAEROBE' THEN 8

ELSE 9

END

) ASC,

b.WHONET\_TEST ASC,

b.SITE\_OF\_INFECTION ASC

### IntrinsicResistance.sql

/\*

Return the set of applicable intrinsic resistance rules according to the conditions applied in the WHERE clause.

\*/

SELECT i.\*, a.\*

FROM Organisms o

INNER JOIN (

SELECT \*,

-- This would need to be expanded if we needed to support more than two exceptions for a single rule (not needed presently).

-- In an application it must be implemented to handle an arbitrary number of items.

substr(EXCEPTION\_ORGANISM\_CODE, 1, instr(EXCEPTION\_ORGANISM\_CODE, ',') - 1) AS [FirstException],

substr(EXCEPTION\_ORGANISM\_CODE, instr(EXCEPTION\_ORGANISM\_CODE, ',') + 1) AS [SecondException]

FROM IntrinsicResistance

) i

ON (

o.SEROVAR\_GROUP IS NOT NULL

AND i.ORGANISM\_CODE\_TYPE = 'SEROVAR\_GROUP'

AND o.SEROVAR\_GROUP = i.ORGANISM\_CODE

) OR (

i.ORGANISM\_CODE\_TYPE = 'WHONET\_ORG\_CODE'

AND o.WHONET\_ORG\_CODE = i.ORGANISM\_CODE

) OR (

o.SPECIES\_GROUP IS NOT NULL

AND i.ORGANISM\_CODE\_TYPE = 'SPECIES\_GROUP'

AND o.SPECIES\_GROUP = i.ORGANISM\_CODE

) OR (

o.GENUS\_CODE IS NOT NULL

AND i.ORGANISM\_CODE\_TYPE = 'GENUS\_CODE'

AND o.GENUS\_CODE = i.ORGANISM\_CODE

) OR (

o.GENUS\_GROUP IS NOT NULL

AND i.ORGANISM\_CODE\_TYPE = 'GENUS\_GROUP'

AND o.GENUS\_GROUP = i.ORGANISM\_CODE

) OR (

o.FAMILY\_CODE IS NOT NULL

AND i.ORGANISM\_CODE\_TYPE = 'FAMILY\_CODE'

AND o.FAMILY\_CODE = i.ORGANISM\_CODE

) OR (

o.ANAEROBE = 'X'

AND i.ORGANISM\_CODE\_TYPE = 'ANAEROBE+SUBKINGDOM\_CODE'

AND ((

o.SUBKINGDOM\_CODE = '+'

AND i.ORGANISM\_CODE = 'AN+'

) OR (

o.SUBKINGDOM\_CODE = '-'

AND i.ORGANISM\_CODE = 'AN-'

))

) OR (

o.ANAEROBE = 'X'

AND i.ORGANISM\_CODE\_TYPE = 'ANAEROBE'

AND i.ORGANISM\_CODE = 'ANA'

)

INNER JOIN Antibiotics a

ON (

i.ABX\_CODE\_TYPE = 'ATC\_CODE'

AND substr(a.ATC\_CODE, 1, length(i.ABX\_CODE)) = i.ABX\_CODE

) OR (

i.ABX\_CODE\_TYPE = 'WHONET\_ABX\_CODE'

AND i.ABX\_CODE = a.WHONET\_ABX\_CODE

) AND (

CASE

WHEN i.GUIDELINE = 'CLSI' AND a.CLSI = 'X' THEN 1

WHEN i.GUIDELINE = 'EUCAST' AND a.EUCAST = 'X' THEN 1

WHEN i.GUIDELINE = 'SFM' AND a.SFM = 'X' THEN 1

WHEN i.GUIDELINE = 'SRGA' AND a.SRGA = 'X' THEN 1

WHEN i.GUIDELINE = 'BSAC' AND a.BSAC = 'X' THEN 1

WHEN i.GUIDELINE = 'DIN' AND a.DIN = 'X' THEN 1

WHEN i.GUIDELINE = 'NEO' AND a.NEO = 'X' THEN 1

WHEN i.GUIDELINE = 'AFA' AND a.AFA = 'X' THEN 1

ELSE 0

END

) = 1

WHERE o.WHONET\_ORG\_CODE = 'sal'

AND o.TAXONOMIC\_STATUS = 'C'

-- AND i.ABX\_CODE = 'VAN'

AND (

-- Organism exceptions to the intrinsic rule, if applicable.

coalesce(i.EXCEPTION\_ORGANISM\_CODE, '') = ''

OR NOT (

(

o.SEROVAR\_GROUP IS NOT NULL

AND i.EXCEPTION\_ORGANISM\_CODE\_TYPE = 'SEROVAR\_GROUP'

AND (

o.SEROVAR\_GROUP = i.FirstException

OR o.SEROVAR\_GROUP = i.SecondException

)

) OR (

i.EXCEPTION\_ORGANISM\_CODE\_TYPE = 'WHONET\_ORG\_CODE'

AND (

o.WHONET\_ORG\_CODE = i.FirstException

OR o.WHONET\_ORG\_CODE = i.SecondException

)

) OR (

o.SPECIES\_GROUP IS NOT NULL

AND i.EXCEPTION\_ORGANISM\_CODE\_TYPE = 'SPECIES\_GROUP'

AND (

o.SPECIES\_GROUP = i.FirstException

OR o.SPECIES\_GROUP = i.SecondException

)

) OR (

o.GENUS\_CODE IS NOT NULL

AND i.EXCEPTION\_ORGANISM\_CODE\_TYPE = 'GENUS\_CODE'

AND (

o.GENUS\_CODE = i.FirstException

OR o.GENUS\_CODE = i.SecondException

)

) OR (

o.GENUS\_GROUP IS NOT NULL

AND i.EXCEPTION\_ORGANISM\_CODE\_TYPE = 'GENUS\_GROUP'

AND (

o.GENUS\_GROUP = i.FirstException

OR o.GENUS\_GROUP = i.SecondException

)

) OR (

o.FAMILY\_CODE IS NOT NULL

AND i.EXCEPTION\_ORGANISM\_CODE\_TYPE = 'FAMILY\_CODE'

AND (

o.FAMILY\_CODE = i.FirstException

OR o.FAMILY\_CODE = i.SecondException

)

) OR (

o.ANAEROBE = 'X'

AND i.EXCEPTION\_ORGANISM\_CODE\_TYPE = 'ANAEROBE+SUBKINGDOM\_CODE'

AND ((

o.SUBKINGDOM\_CODE = '+'

AND (

i.FirstException = 'AN+'

OR i.SecondException = 'AN+'

)

) OR (

o.SUBKINGDOM\_CODE = '-'

AND (

i.FirstException = 'AN-'

OR i.SecondException = 'AN-'

)

))

) OR (

o.ANAEROBE = 'X'

AND i.EXCEPTION\_ORGANISM\_CODE\_TYPE = 'ANAEROBE'

AND (

i.FirstException = 'ANA'

OR i.SecondException = 'ANA'

)

)

)

)

ORDER BY i.GUIDELINE ASC,

(

CASE i.ORGANISM\_CODE\_TYPE

WHEN 'SEROVAR\_GROUP' THEN 1

WHEN 'WHONET\_ORG\_CODE' THEN 2

WHEN 'SPECIES\_GROUP' THEN 3

WHEN 'GENUS\_CODE' THEN 4

WHEN 'GENUS\_GROUP' THEN 5

WHEN 'FAMILY\_CODE' THEN 6

WHEN 'ANAEROBE+SUBKINGDOM\_CODE' THEN 7

WHEN 'ANAEROBE' THEN 8

ELSE 9

END

) ASC,

(

CASE i.ABX\_CODE\_TYPE

WHEN 'WHONET\_ABX\_CODE' THEN 1

WHEN 'ATC\_CODE' THEN 2

ELSE 3

END

) ASC,

i.ABX\_CODE ASC,

a. WHONET\_ABX\_CODE ASC