Proposed modifications to EUCAST definition of the intermediate category

Detailed below are proposals to modify EUCAST definition of the intermediate category. The proposals are open for comment by 3 December 2015.

Please send comments, with supporting data or references where appropriate, to the EUCAST Scientific Secretary (derek.brown222@btinternet.com). Please use the accompanying form for your comments.

Background
The original EUCAST definition included the various traditional uses of the intermediate category:

“A microorganism is defined as intermediate by a level of antimicrobial agent activity associated with uncertain therapeutic effect. It implies that an infection due to the isolate may be appropriately treated in body sites where the drugs are physiologically concentrated or when a high dosage of drug can be used; it also indicates a buffer zone that should prevent small, uncontrolled, technical factors from causing major discrepancies in interpretations.”

The inclusion of multiple definitions for the intermediate category results in it being interpreted differently by different groups and has led to confusion regarding its meaning. Use of the intermediate category as a buffer zone because of technical variation is an entirely different meaning to the use of intermediate as a category where treatment is possible because the agent is physiologically concentrated or an increased dosage is possible.

The EUCAST emphasis on avoiding the division of wild type populations when setting breakpoints has reduced the need for a buffer zone and for several years EUCAST has not used the concept of a buffer zone when setting new breakpoints or when revising breakpoints. Hence there are now many agents and species where EUCAST has not included an intermediate category.

If it were decided to keep the concept of a buffer zone in the definition, it would be logical to use an intermediate category with all breakpoints as there is always some technical variation in antimicrobial susceptibility tests. The idea of avoiding “major errors” (reporting S as R) and “very major errors” (reporting R as S) by including an intermediate category is attractive and a wide intermediate category would make such errors rare, but with a significant part of the population in the intermediate category. In practice, intermediate becomes a “don’t know” category which is generally interpreted as resistant by clinicians.

The following proposed revised definitions remove the concept of a technical buffer zone from the definition of intermediate category and include some typographical changes.
Definitions of clinical breakpoints and the epidemiological cut-off value

1. Clinical breakpoints

**Susceptible (S)**
A microorganism is defined as susceptible by a level of antimicrobial activity associated with a high likelihood of therapeutic success.

**Intermediate (I)**
A microorganism is defined as intermediate by a level of antimicrobial activity associated with a high likelihood of therapeutic success but only when a higher dosage of the agent than normal can be used or when the agent is physiologically concentrated at the site of infection.

**Resistant (R)**
A microorganism is defined as resistant by a level of antimicrobial activity associated with a high likelihood of therapeutic failure.

Notes
1. Microorganisms are categorized as S, I or R by applying breakpoints in a defined phenotypic test system
2. Clinical breakpoints are presented as $S \leq x \text{ mg/L}; I > x, \leq y \text{ mg/L}; R > y \text{ mg/L}$
3. The EUCAST standard and high doses for agents are shown on the last page of the EUCAST breakpoint tables.
4. "High-dose" may relate to a larger amount of the agent with the same frequency as the normal dose, a higher frequency of dosing or prolonged infusion.
5. Clinical breakpoints are subject to review and revision when circumstances change. The change may be in dosing, routes of administration and new resistance mechanisms.

2. Epidemiological cut-off values (ECOFFs)

**Wild type (WT)**
A microorganism is defined as WT for a species by the absence of phenotypically detectable acquired and mutational resistance mechanisms to the agent in question.

**Non-wild type (NWT)**
A microorganism is defined as NWT for a species by the presence of phenotypically detectable acquired or mutational resistance mechanisms to the agent in question.

Notes
1. A microorganism is categorized as WT or NWT for a species by applying the appropriate cut-off value (ECOFF) in a defined phenotypic test system.
2. NWT microorganisms harbour one or more resistance mechanisms but, depending on the values of the clinical breakpoints, WT and NWT microorganisms may or may not respond clinically to treatment with the agent.
3. The wild type is presented as $WT \leq z \text{ mg/L}$ and non-wild type as $NWT > z \text{ mg/L}$ (where $z$ is the ECOFF). For a species and an antimicrobial agent the ECOFF is the highest MIC value for isolates devoid of phenotypically detectable resistance mechanisms.
4. The ECOFF will not be altered unless accumulated additional MIC distributions indicate the need for an adjustment.
Comments on proposed modifications to the EUCAST definition of the intermediate category,
October 2015

Please send any comments on these proposals, with supporting data or references where appropriate, to the EUCAST Scientific Secretary (derek.brown222@btinternet.com) before 3rd December 2015. Please use this form for your comments.

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<tr>
<th>Comment from (name, contact details)</th>
<th>Comments</th>
<th>EUCAST responses</th>
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<tr>
<td>Jean B. Patel</td>
<td>I don’t agree with the proposal to remove technical variability from the definition of intermediate. Antimicrobial susceptibility testing methods described by EUCAST, CLSI and ISO (basically the same methods) demonstrate technical variability. This is easiest to identify by looking at ranges for QC strains (i.e., the range is the technical variability for one bug/drug combination after many rounds of testing). Failure to include technical variability in the intermediate definition will result in too many false resistant results and the exclusion of effective therapeutic agents from being used as therapy.</td>
<td>1. Agreed that there is technical variation in antimicrobial susceptibility testing. Inclusion of technical variation in the definition of the intermediate category does not eliminate the effects of technical variation. Including an intermediate category just to accommodate variation does not stop effective agents being excluded from use because if organisms are defined as intermediate the agent is likely to be excluded from use unless a higher dosage is approved (included in the summary of product characteristics). EUCAST has rarely (&lt;10% of intermediate categories) included an intermediate category to reduce categorical errors. Hence the intermediate category has mostly been used to signal the need for a higher dose or, when the entire wild type distribution has been included in the intermediate category, to signal the need for the highest accepted dose in the treatment of infections caused by the species. Adding intermediate categories for all antimicrobial agents would reduce the number of categorical errors (major and very major errors), but would instead move the uncertainty to the clinicians. Clinicians commonly refrain from using agents reported as intermediate as they equate it with uncertainty and systematically including intermediate categories with all breakpoints would further encourage clinicians to equal “intermediate” and “uncertain” and would in effect remove the high dose and physiological concentration definitions from the intermediate category. This is not in</td>
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If breakpoints are set within the wild type there will be unacceptable variation as the wild type distribution is largely a result of technical variation. Inclusion of an intermediate category does not overcome the problem. Avoiding splitting the wild type often does, as the breakpoint does not fall in the region of the susceptibility distribution that includes most isolates. EUCAST systematically aims to avoid splitting wild type distributions when setting breakpoints.

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<td>Christoffer Lindemann, NWGA –scientific secretary, <a href="mailto:pc-linde@online.no">pc-linde@online.no</a></td>
<td>The NWGA are generally pleased with the proposed change in definition. However, we feel the use of the term &quot;higher dosage of the agent than normal&quot; is unprecise and not consistent with the terms used for instance in the breakpoint table. We would therefore suggest a small change in the definition: “…but only when a higher than standard dosage of the agent can be used….”</td>
<td>2. Agreed.</td>
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<td>Pr Patrice COURVALIN, MD, FRCP</td>
<td>A suggestion in the text on ECOFFs: Please delete &quot;and mutational&quot; since acquired covers horizontal gene transfer and maturational events. Independently, we are sending our comments. with the colleagues at Zurich, on the intermediate category.</td>
<td>3. Agreed.</td>
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<td>FiRe</td>
<td>FiRe is worried about the proposal to delete the buffer zone concept from the definition of the intermediate category. From the point of view of clinical laboratories carrying out and controlling the AST, the buffer zone function is included in line with the intention of EUCAST.</td>
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the definition with good reason.

Even when the standard is strictly followed, AST involves uncertainty and imprecision which should not be ignored. With disc diffusion, the minimum variability in measured inhibition zone diameters is 2-3 mm when the zone diameters are in the 18-30 mm range, where also many breakpoints are situated. The imprecision does not cause major problems if the zone diameters of susceptible and resistant populations of a given bacterial species are clearly separated by an area with few strains between them. However, many resistance mechanisms result in gradual change in the diameters or MIC values, and thus many strains lie in close vicinity to any breakpoint. The lack of an intermediate category in these cases inevitably results in frequent major and very major errors (see e.g. H. influenzae disc diffusion zone diameter distribution for amoxicillin-clavulanic acid).

The clinical laboratory standard ISO 15189 obliges laboratories to consider measurement uncertainty when interpreting measured quantity values (5.5.1.4). Intermediate category is an established expression of uncertainty (uncertain therapeutic effect) and should remain so. “High likelihood of therapeutic success but only when a higher dosage of the agent than normal can be used” suits only in about one third of current drug-bacteria combinations with intermediate category. If the aim of the change is to reduce confusion in interpreting the laboratory reports, the above message would be more clearly expressed by Susceptible –dose dependent, which is used by CLSI for some antifungal agents.

4. All tests have some variation. When the breakpoint falls in an area where there is a range of susceptibility attributable to multiple resistance mechanisms or variable expression of resistance mechanisms, variation cannot easily be avoided and an intermediate category will help to reduce major and very major errors. It is then a balance of widening the intermediate category to reduce major and very major errors at the expense of effectively excluding an increasing population from treatment.

5. The ISO standard does require laboratories to consider measurement uncertainty. In categorical interpretation, this is partly covered by setting breakpoints that do not divide the wild type distribution. The WT distribution includes biological variation and measurement errors. The intermediate category gives no measure of uncertainty. One of the main reasons for suggesting a change in the definition of the intermediate category is because the definition has four different meanings embedded in the current definition but the clinician is never advised as to which of these apply to a specific intermediate result.

6. “Susceptible dose dependent” is an odd designation as all breakpoints are dose dependent. Maybe it would be better defined as “susceptible high dose”. This encompasses >90% of current EUCAST intermediate
We have read with great interest the modifications proposed by EUCAST for the definition of the intermediate category. There is a long-lasting misperception of the intermediate category, namely that the “intermediate” category would only be necessary to accommodate technical variation. In fact, the intermediate category reflects biological diversity, e.g. overlapping wild-type and non-wild-type populations. The statement that “the EUCAST emphasis on avoiding the division of the wild type population when setting breakpoints has reduced the need for a buffer zone” is not supported by scientific data as uncontrolled technical factors and biological variability will not disappear by this approach (1).

In brief, we suggest the following:

i) Keep the dual definition of the intermediate category for therapeutic AND technical aspects, not the least with the view to reflect the biological variability. It is not reasonable to pretend accuracy, which is not present. We would like to emphasize that the statement in the EUCAST proposal “including […] a wide intermediate category would make such errors rare, but with a significant part of the population in the intermediate category” is not supported by published data (1). For example, an intermediate zone of only 3 mm would avoid categorisation errors. If separate designations are used for susceptible high dose and “indeterminate because of variation” it would be logical to include intermediate categories between susceptible and susceptible high dose, and between susceptible high dose and resistant, i.e. five susceptibility categories. This is clearly impractical from both a technical and a clinical point of view.

7. If there were no technical variation there would be no argument for an intermediate category other than to indicate a higher dosage or physiological concentration of the agent. Avoiding splitting the wild type when possible reduces the effect of uncontrolled variation but it has never been suggested that technical variation will disappear. Biological variation resulting in variable susceptibility is discussed in response 4.

8. The effect of an intermediate category depends on where in the distribution the intermediate category is placed. A 3 mm intermediate category outside the wild type in a sparsely populated area of the zone diameter distribution may avoid most major and very major categorisation errors, but this is certainly not the case if the intermediate category falls within the wild type.

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virtually all categorization errors for the majority of species-drug combinations and an intermediate zone of only 3 mm can hardly be considered as “wide”.

ii) AST reports should indicate MIC and diameter measurements in combination with reference ranges and laboratory measurement precision data, enabling clinicians to assess the reliability of clinical categorization (2).

iii) AST reports would benefit from inclusion of an indicator of interpretation reliability, e.g., percentages of probability for correct clinical classification based on EUCAST and/or CLSI clinical breakpoints. These probabilities would reflect the AST forecast reliability for clinical outcome, facilitating the selection of the most adequate drug for treatment (2).

The confidence of clinicians in microbiological reports will not be strengthened by claiming precision in clinical categorization that, on one hand, seems less ambiguous (only S and R categories), but on the other hand produces frequent S/R discrepancies; Enhancing the precision of measurements by significant reduction of the technical variation would improve AST accuracy (3, 4, 5). As long as highly precise measurements cannot be achieved in the majority of the clinical laboratories, we propose to include indicators of technical measurement reliability in clinical reports. We would appreciate to exchange on these relevant and practical questions with EUCAST.

9. This may be an ideal but it is unlikely that this would be practical or within the capabilities of most LIMS. Expectations of clinicians vary between countries but, from first-hand experience, many would not welcome more data and would prefer a clear indication of whether the isolate is susceptible or resistant, (although this is increasingly not so clear cut. The suggested approach would perhaps work for a small fraction of particularly well-informed clinicians with laboratory experience, but not for the vast majority.

10. Again an ideal that is unlikely to be practical. It also assumes that the quality of testing is the same in all laboratories and this is clearly not the case.

11. Reference to “only S and R categories” implies that there may be a misunderstanding. EUCAST is not suggesting removal of the intermediate category, but only to limit the definition of the intermediate category to clearly signal the need for a higher dose.
and are looking forward to the continued discussion on this issue.

Sincerely,
Michael Hombach,
Erik C. Böttger
Patrice Courvalin

Literature cited:
We are writing in response to the call for comments on the recently posted document “Proposed modifications to EUCAST definition of the intermediate category.” We are grateful for the opportunity to provide input into this proposed change in policy. Let us start by saying that we appreciate the intent behind this proposal. The “I” category has long been a source of confusion. However, we have two categories of concerns regarding your proposal.

First, we have a group of technical concerns:

- Will EUCAST leave all of the existing “Intermediate” categories in the EUCAST tables, and only implement this proposed definition going forward for new drugs or for drugs for which breakpoints are changed?
- If EUCAST plans to leave agents with existing “Intermediate” categories in the table of clinical breakpoints, does that mean that all of the “Intermediates” are now to be considered “Breakpoints relating to High Dose Therapy?” We are concerned that not all of the “Intermediates” in the table were set with a possibility of a higher dosage (approved across all indications), and therefore leaving all of the old “Intermediate” category assignments may lead to confusion about which drugs do and do not have the option for a higher dose and for which indication, if not available for all.

- If EUCAST does not plan to leave all of the “Intermediates,” then will the current “Intermediate” category become “Resistant?” We are concerned with this approach, as many drugs have had “Intermediate” dilutions set not only as a buffer for testing, but as a sort of compromise between what is included in the WT distribution and what is covered by PK/PD, but where there was no clinical evidence to

12. More than 90% of the EUCAST intermediate categories relate to a higher dose than the standard dose on which the susceptible breakpoint is based. In addition a few full wild type distributions were placed in intermediate to signal the need for the highest dose possible for infections caused by the species in question (e.g. currently ciprofloxacin and Streptococcus pneumoniae, aztreonam and Pseudomonas aeruginosa). Where there are discrepancies (an intermediate category without a high dose) these will need to be resolved as soon as possible.

13. We encourage examples to be given but believe that you are referring to the situations where the entire wild type distribution of a species was categorised as intermediate to signal the need for the highest possible dose (this is currently the case for none of the Enterobacteriaceae breakpoints, one of the Pseudomonas breakpoints, six of the H. influenzae breakpoints and one of the S. pneumoniae breakpoints. Obviously EUCAST will need to resolve these
allow a higher “Susceptible” breakpoint. We are also concerned that changing current “Intermediates” to “Resistant” will lead to false reports of resistance. We encourage EUCAST to consider defining another term, such as “Non-Susceptible” in such cases, rather than categorize these organisms as “Resistant” to clearly distinguish between organisms shown to harbor well characterized resistance mechanisms from those that fall outside of clinical experience.

• The current EUCAST table of clinical breakpoints already lists some agents with “Susceptible” categories labeled as “Breakpoints relate to High Dose Therapy.” How would these be distinguished from the new “Intermediate” category? These existing comments may need to be clarified in the table.

• Will the revised definition of “Intermediate” apply to antifungal agents as well? The discussions of “Intermediate” in the rationale documents for anidulafungin and micafungin give different interpretations of the meaning of “Intermediate” and the idea of using a higher dose does not seem to apply.

• We are concerned that the elimination of “Intermediate” also removes the buffer zone that is often needed to manage the inherent variability in MIC tests. We suggest that EUCAST consider that there may be an ongoing need for such a buffer zone for some drugs. For example, piperacillin-tazobactam is discrepancies as soon as possible but some may be left in the intermediate category since this will continue to encourage the use of “high dose” and will in fact fit with the more restricted definition planned for the future.

EUCAST do not see any value in defining additional categories such as “non-susceptible”. In practice this is not helpful and is no different to reporting resistant.

14. EUCAST acknowledges that there is some inconsistency here. In some cases a wild type distribution is designated susceptible with a recommendation in a note in the table to use the highest possible dose whereas in other situations the wild type is designated intermediate, which in itself stipulates the use of a high dose. The difference between the two, as it developed over the years, is that the former is used when there is a good possibility of treatment success and a strong tradition of using the agent to treat infections caused by the indicated organism, whereas for the latter there is some doubt about the outcome of using high doses.

15. The revised designations have been based on breakpoints for bacteria. When the definition has been agreed for bacteria the subcommittee on antifungal susceptibility testing will be consulted about possible implications for antifungal agents.

16. We agree that there are some organism-agent combinations where tests are particularly variable. This will be considered in further discussions but may indicate that the breakpoints need adjusting to accommodate the additional variation, that the agent is inappropriate for use against that organism, or that the particular test is unreliable.
well known for demonstrating day to day variability in testing. Also, when one considers QC histograms for one drug- one organism combinations, there is almost always variability over several dilutions. Please also note that many older drugs will have substantial numbers of isolates at the breakpoint and therefore may test “Susceptible” on Day 1, then “Resistant” on successive days, but in fact, no resistance has developed.

Second, we have a broader concern about problem of communicating the idea of Intermediate as a zone in which a higher dose would have activity. Even though intention behind the proposed change in EUCAST’s policy for the meaning of the “Intermediate” category is clear to us as experienced microbiologists, we are concerned that “Intermediate” will continue to be interpreted as “I don’t know what this means” for the end users of the breakpoints such as the physician receiving the microbiology report for patient care. Stated differently, we think that practical experience has shown that the abbreviation “I” is ambiguous and lacks the clarity of meaning associated with “S” and “R”.

As an alternative approach, we recommend that EUCAST give consideration to the designation of “Susceptible, Dose-Dependent” (SDD) that has been used by CLSI. In our view, the concepts underpinning SDD and EUCAST’s new definition of “Intermediate” are essentially the same. Use of this PK-PD-linked designation was discussed at the recent EMA workshop on their draft PK/PD guidance document as a way to enhance communication between the laboratory and the treating physician. A further advantage of using SDD is that it encourages the recipient of the
microbiology report to shift from “I don’t know” into “I should seek advice.” Therefore, we encourage EUCAST to consider a different designation for the “Intermediate” category that is meant to refer only to susceptibility to a higher dose. The simplest thing would be to harmonize with the other agency and use SDD, but a term different from both SDD and “Intermediate” would also be acceptable. This would eliminate any further confusion about what “Intermediate” means.

In closing, we’d like to again thank you for the opportunity to provide comments on this idea. Our principal concern is that the change has a high risk of creating confusion in an already confusing area. Please let us know if you have any questions, or would like clarification on these comments. If a decision is made to change the “Intermediate” designation, the change will require a great deal of education for the end user of the breakpoints. We encourage EUCAST to be very proactive in this education process.

<table>
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<tr>
<th>Robin Howe</th>
<th>The proposal to remove the concept of a buffer zone is accepted.</th>
<th>18. No response needed.</th>
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<tr>
<td>BSAC</td>
<td>The proposal to remove the concept of a buffer zone is accepted.</td>
<td>18. No response needed.</td>
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<td>SRGA understands and acknowledges the need for clarifying the differences between the different definitions of the I-group (native population in I-group, buffer zone, physiological concentration, higher dosage). However, we see at least two potential problems with implementing the definition now:</td>
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<td>a) There are several examples of I-groups that are not in line with the new definition in the current breakpoint table. It is our belief that the new I-definition should not be implemented before the table has been amended properly</td>
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<td>19. See note 12.</td>
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b) We do not believe that the need for a buffer category will disappear, in particular with many new breakpoints being set so that they actually cleave a part of the wild-type population (e.g. Pseudomonas and colistin, tigecycline and some species of Enterobacteriaceae). It is possible that the optimal term for this group is not intermediate, but we find it likely that some type of buffer will still be needed in the future, and that this is not addressed in the new system. Perhaps a new category could be called “uncertain outcome” or something similar.

At the end it will of course be necessary for the labs to provide a helpful answer to clinicians, but it would be at least be good for the labs to have a methodological buffer zone for those situations where for example repeat testing may be warranted.

Also, alternative strategies could be considered. The need for higher dosage may be communicated to clinicians without using the I-group by making certain specified entities of drug dosage (e.g. Benzylpenicillin high dosage) in accordance with those now used in the EUCAST table for infection site (e.g. Benzylpenicillin meningitis) or administration (e.g. Cefuroxime p.o). This may also facilitate appropriate selection of drug since many clinicians tend to only use drugs defined as “S”.

20. See note 16. For special cases (e.g. ceftaroline vs MRSA, piperacillin-tazobactam vs. Enterobacteriaceae), where testing is extremely difficult introduction of an “Area of Technical Uncertainty” has been discussed. It will be an area of overlap between S and R where further testing may achieve reproducible categorisation. It would function as a warning to the laboratory and will most likely not appear in the report.
Conclusion
The detailed and perceptive comments are appreciated. However, the current definition remains highly unsatisfactory as it is interpreted in at least four different ways without a signal to the clinician as to which applies in individual cases. EUCAST has only rarely used intermediate as "a buffer zone" to avoid major and very major errors and has rarely used the intermediate category unless a higher dose can be used. There is a need for further consideration before any changes are made and the current definition will not be changed without further wide consultation.