Le problème des normes de référence en auto-immunité

Jean-Paul Tomasi
Responsable du laboratoire d'auto-immunité
CU St Luc, Bruxelles

Rheumatoid factor & Anti-CCP

- The new classification criteria (2010) for
- Rheumatoid Arthritis make the distinction
- between

- weakly and strongly positive results.
- It is highly recommended to use a
- quantitative method for both tests

New criteria for early diagnosis of rheumatoid arthritis (ACR/EULAR 2010)

Table 2 – The 1987 revised American College of Rheumatology criteria for the classification of RA[a]

Criterion	Definition
1. Morning stiffness for 6 weeks	Morning stiffness of joints lasting at least 1 hour before maximal improvement
2. Arthritis of 3 or more joint areas for 6 weeks	At least 3 joint areas simultaneously have soft tissue swelling or fluid observed by physician
3. Arthritis of hand joints for 6 weeks	At least 1 joint area swollen (as in criterion 2) in the wrists, MCP joints, or PIP joints
4. Symmetrical arthritis for 6 weeks	Simultaneous involvement of the same joint area (as in criterion 2) on both sides of body
5. Rheumatoid nodules	Subcutaneous nodules over bony prominences or extensor surfaces, or around joints
6. Serum rheumatoid factor	Presence of abnormal amounts of rheumatoid factor by any method, with < 5% in controls
7. Radiographic changes	Changes typical of RA on hand and wrist radiographs, such as erosions and periarticular osteopenia

RA, rheumatoid arthritis; MCP, metacarpophalangeal; PIP, proximal interphalangeal.

[a] A patient is said to have RA if at least 4 of the 7 criteria are present.

Data from Saraux A et al. *Arthritis Rheum*. 2001.[12]

Joint involvement (0-5)

1 med / large joint	0
2-10 med / large joints	1
1-3 small joints	2
4-10 small joints	3
>10 joints (at least 1 small)	5

Serology (0-3)

Neither Rf nor ACPA positive	0
At least one test low postive	2
At least one test high postive	3

Duration of synovitis (0-1)

<6 weeks	0
>6 weeks	1

Accute phase reactants (0-1)

Neither CRP nor ESR abnormal	0
Abnormal CRP or abnormal ESR	1

New criteria for early diagnosis of rheumatoid arthritis (ACR/EULAR 2010)

- The new criteria ACR / EULAR therefore give the ability **to diagnose the disease earlier** and allow doctors to offer a substantive treatment earlier during its evolution.

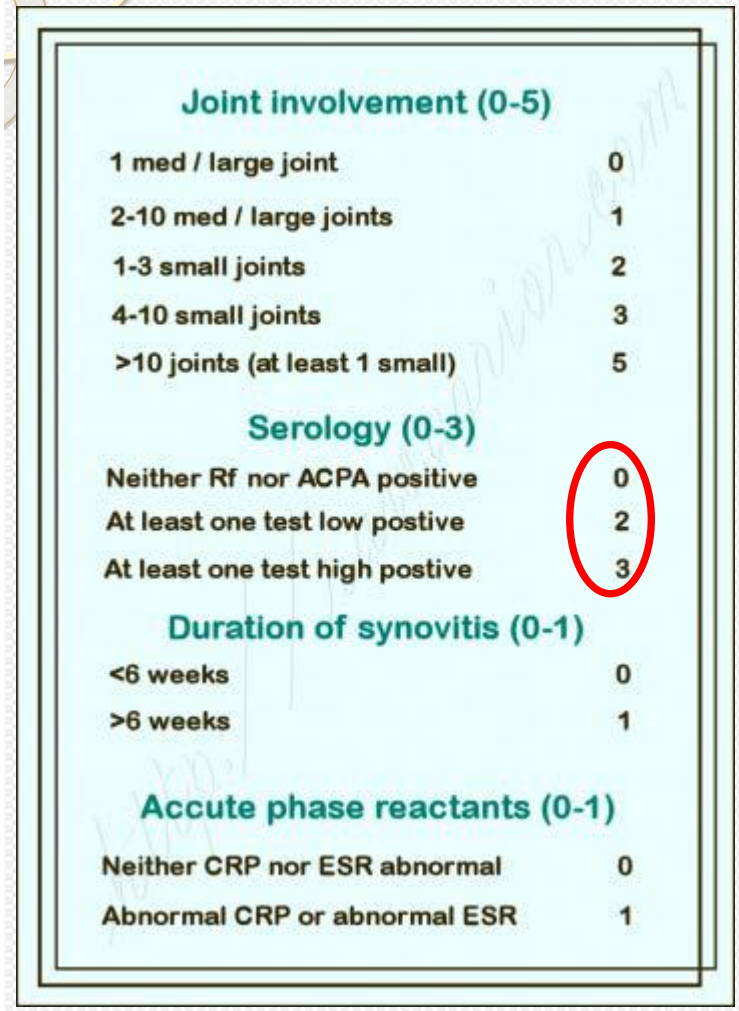
New criteria for early diagnosis of rheumatoid arthritis (ACR/EULAR 2010)

- Even if 'positive' response may still be considered acceptable interpretation **for the 2 parameters**, it is advised to follow the following definitions to "low positive“ and "strongly positive"

New criteria for early diagnosis of rheumatoid arthritis (ACR/EULAR 2010)

- A result is considered weakly positive if its value is **1 to 3 times** the equivalent of the limit value
- A result is considered positive if its value is greater than **3 times** the limit value

New criteria for early diagnosis of rheumatoid arthritis (ACR/EULAR 2010)



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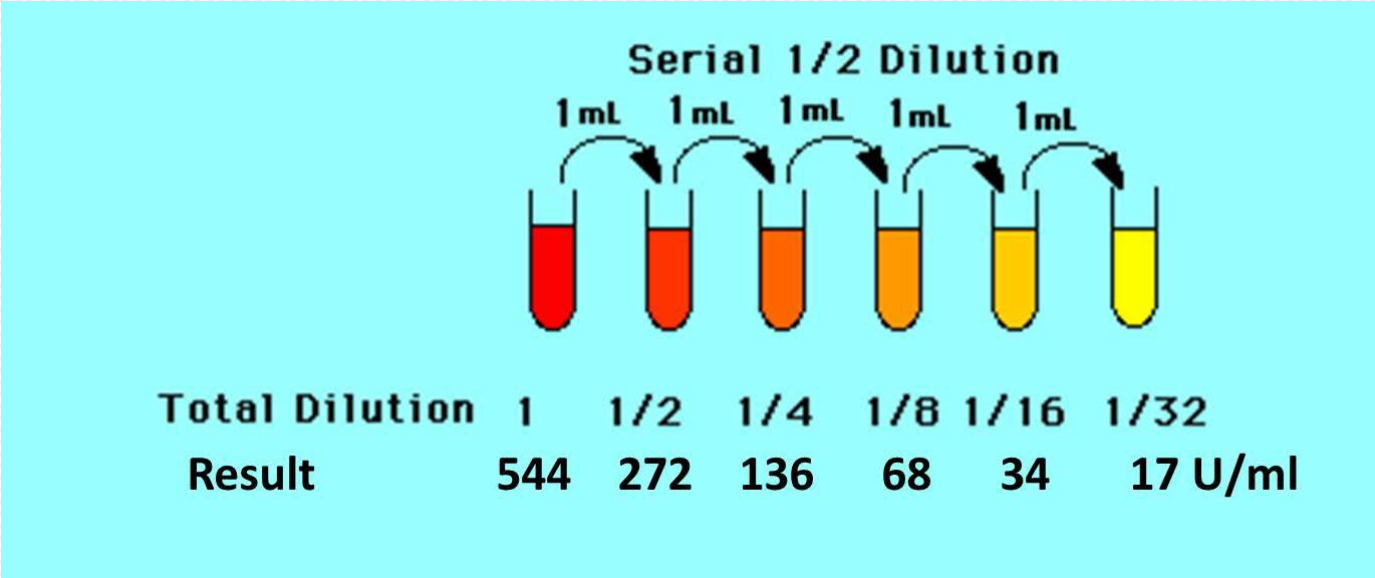
- To diagnose a disease as rheumatoid arthritis, a score ≥ 6 is necessary.
- It is advisable to introduce these guidelines during the reporting of the results.

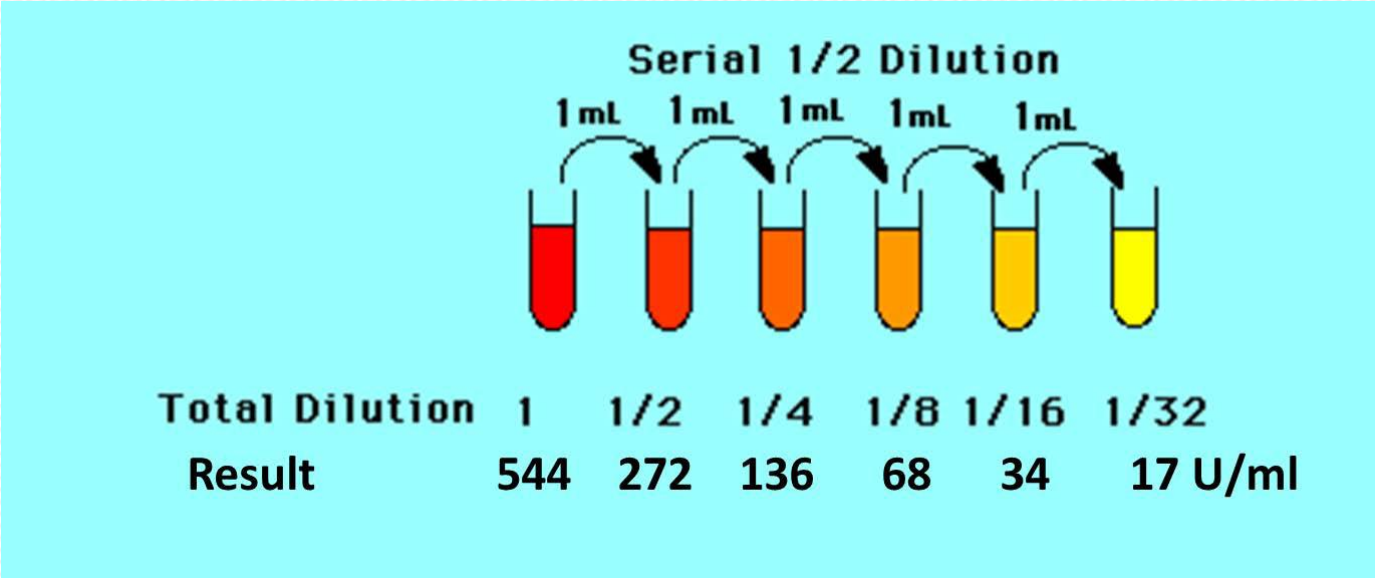
Rheumatoid factor

- Methods that use a standard, to transform the titers in U/mL, are not recommended
- Example : Standard = 544 U/ml



Rheumatoid factor

- This practice gives wrong impression of a continues series of data which is not the case!



Rheumatoid factor

- In conclusion, for several reason, it is highly recommended to quantify RF using
- a quantitative method
- with an operator independent reading

Rheumatoid factor

- It is worth noting that the number of labs still using titration and visual readings is in sharp decline

Rheumatoid factor

- At the very least, results obtained with serial dilutions of the sample must be compared to results obtained by
- **other users of the same method**
- **and quantitative methods (U/mL)**

Anti-CCP Test results obtained with different kits are NOT comparable !

- Abbott - Architect Anti-CCP Abbott - AxSYM Anti-CCP Aesku Diagnostics - Aeskulisa CCP DiaSorin - Anti-CCP Diesse Diagnostica - Other Diesse Diagnostica - RA/CP-Detect Euro-Diagnostica - Immunoscan CCPLUS Euroimmun - Anti-CCP ELISA (IgG) Inova - Quanta Lite CCP3 IgG ELISA Inova - Quanta Lite CCP3.1 IgG/IgA Phadia - EliA CCP Phadia - Other Roche - Anti-CCP Siemens - Immulite 2000 Anti-CCP IgG …

Differences concern (among other things) :

- Calibrators values
- Units
- Cut-off value
- Mode of calculation
- …

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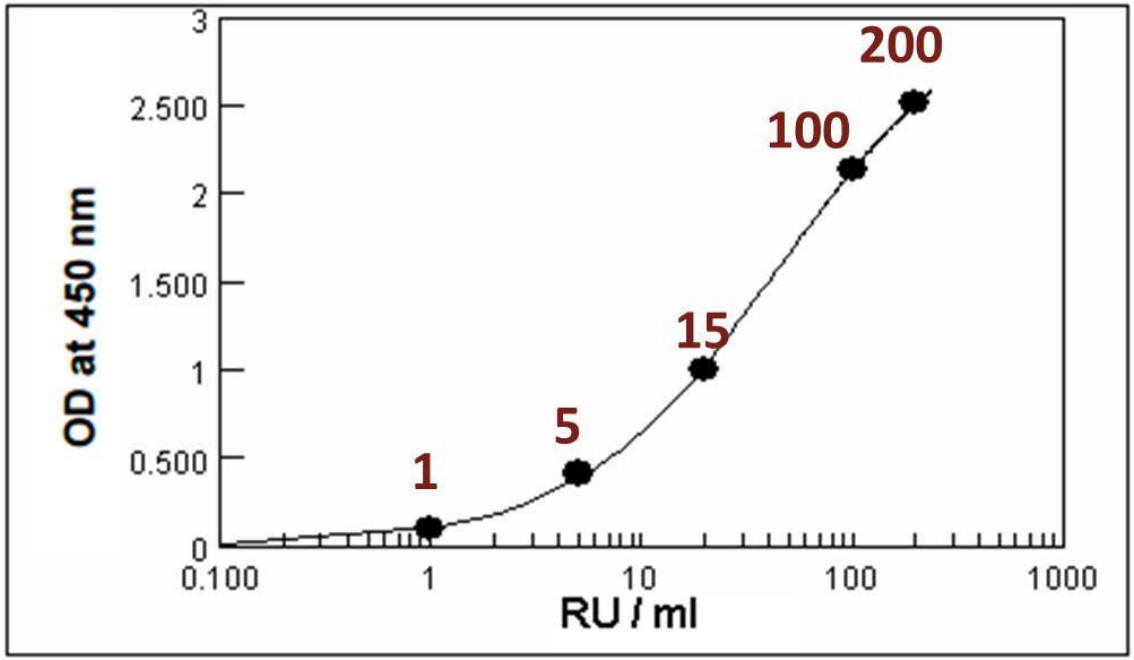
Interpretation of Results

- Before you perform your statistical analysis (reproducibility, CV%, etc…), you must convert the data of one axis to match that of the other.



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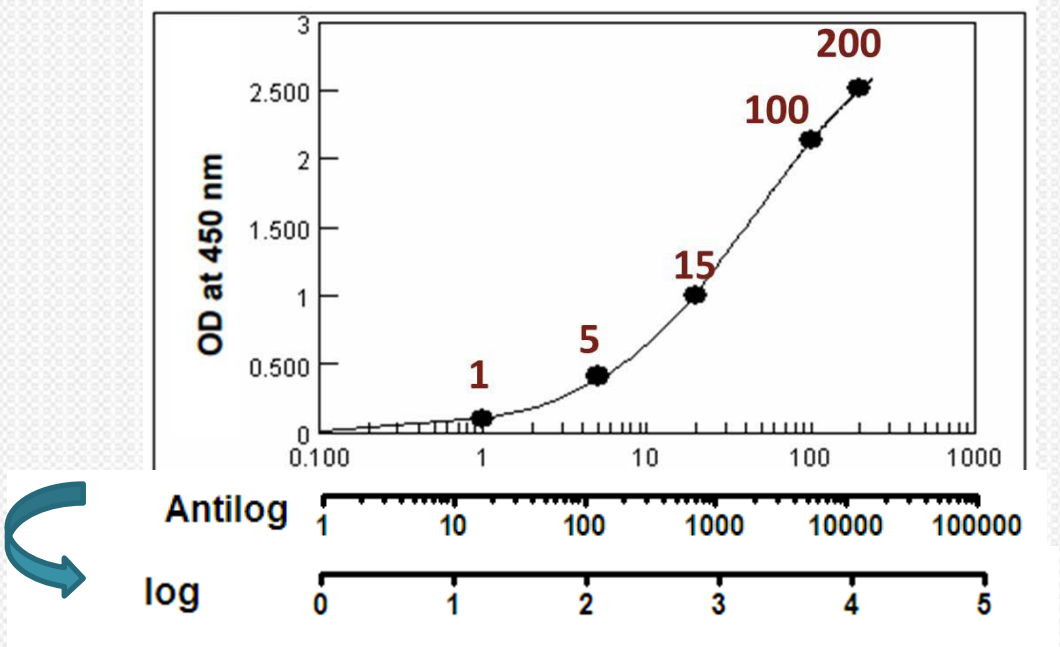

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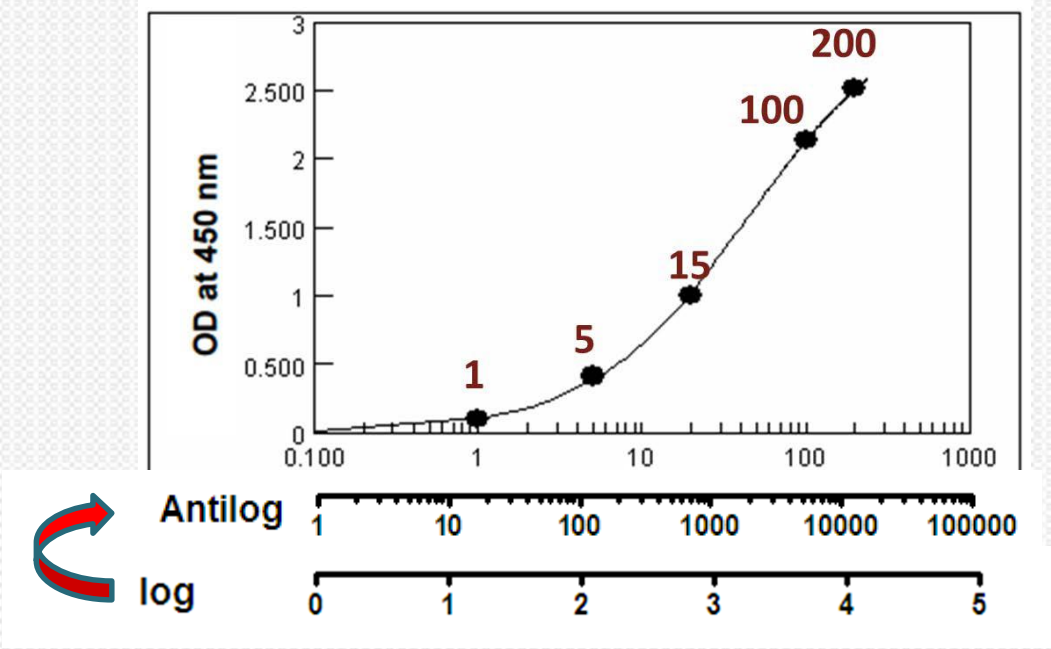

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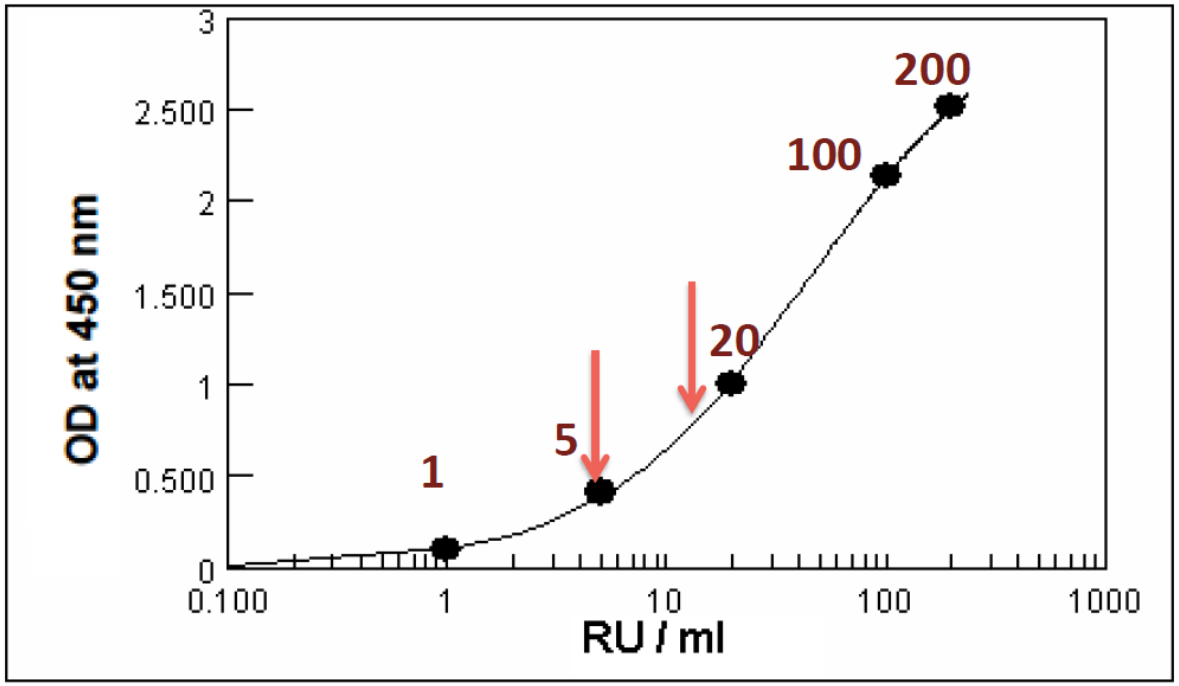
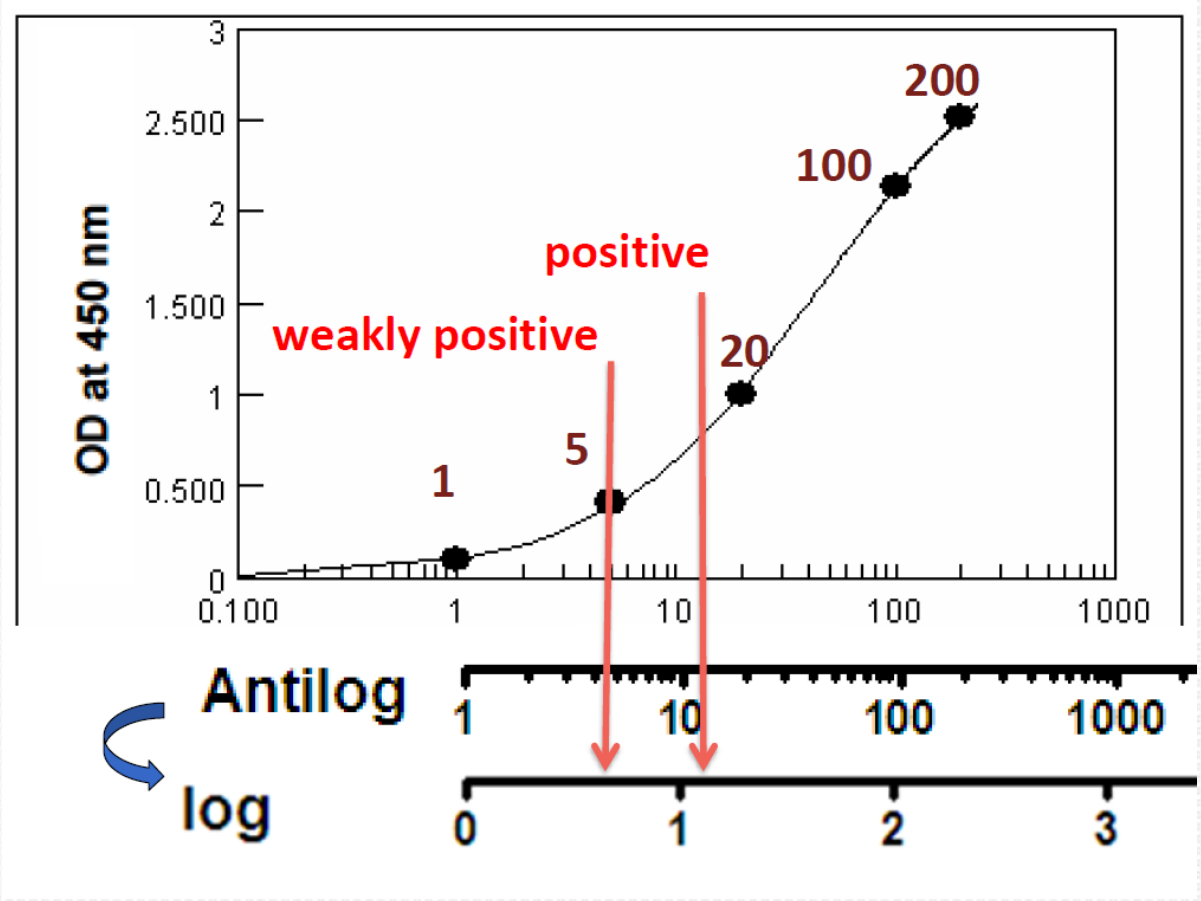
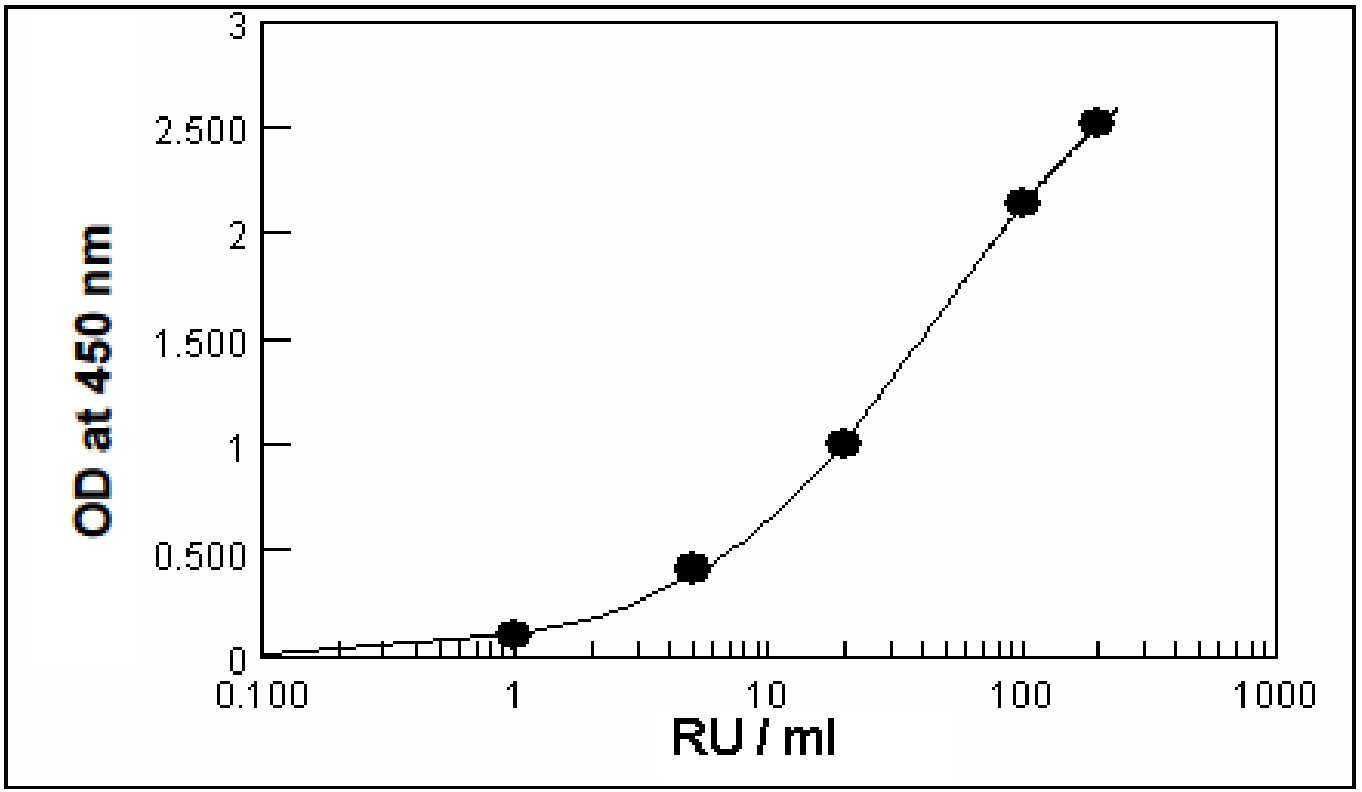


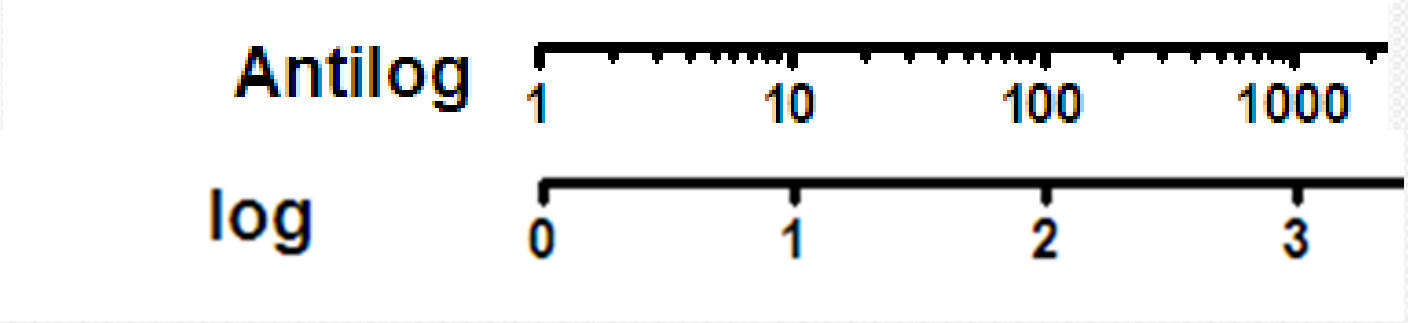
Interpretation of Results

log 5 = 0,7 log 15 = 1,176

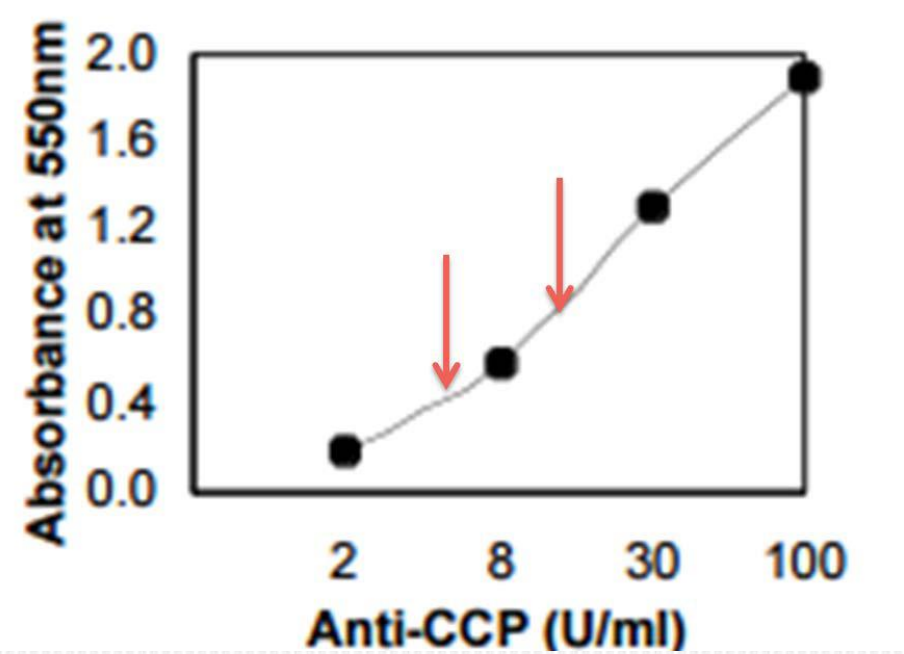


In this example, the base of the logarithms is well defined and constant (base 10)





Another kit with the same cut-off but others calibrators and mode of calculation :
5 RU/ml weakly positive
above 15 RU/ml positive



- In this example, the base of the logarithms is not defined and variable
- (base 2 -> 10 ?)

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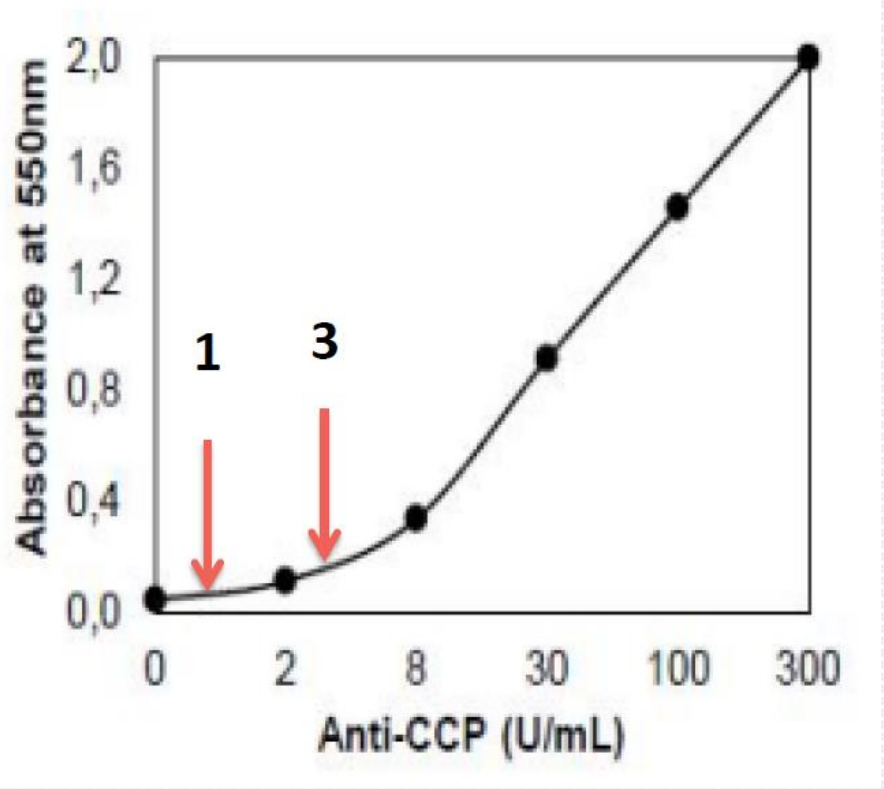

- In this example, the base of the logarithms is not defined
- (base 2 -> 3)

Conclusion

- The problem of lack of standardisation of the anti-ccp tests must not be underestimated.
- The solution to assay variability is complex.
- Individual biologists need to be educated to ensure that they always use the same kit, standards, and mode of calculation for patient investigation

Conclusion

- Anti-ccp standardisation will contain at least following three aspects, if not more:
- 1. Reagent standardization process
- 2. Uniform cut-off value and units
- 3. Similar computerised mode of calculation
- **Lastly, the issue may even be ethical**

Thank you for your attention!