POCT bilirubin management in neonates

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Satellite Meeting

WORLDLAB · EUROMEDLAB ROMA 2023

Point-of-Care Testing: Home, Hospital and Beyond

May 20-21, 2023 "La Nuvola" Roma Convention Center, Rome, Italy

Clinical contexts, analytical devices and challenges

About neonatal bilirubinemia

Bilirubin in neonates
Clinical Contexts

- In pediatrics, **accurate measurement of total serum bilirubin** (TSB) is of major importance for reliable diagnosis and appropriate management of neonatal jaundice
- **Clinical indications**
  - ➢ **Screening of neonatal kernicterus**
  - ➢ **Clinical decision of treatment initiation**
    - ✓ therapeutic indication curves (phototherapy and exchange transfusion) based on the total bilirubin (BTS) blood assay
  - ➢ **Treatment follow-up**
  - ➢ **Decision to leave** the maternity ward
  - ➢ **Follow-up after leaving** the maternity ward (HAS recommendation)

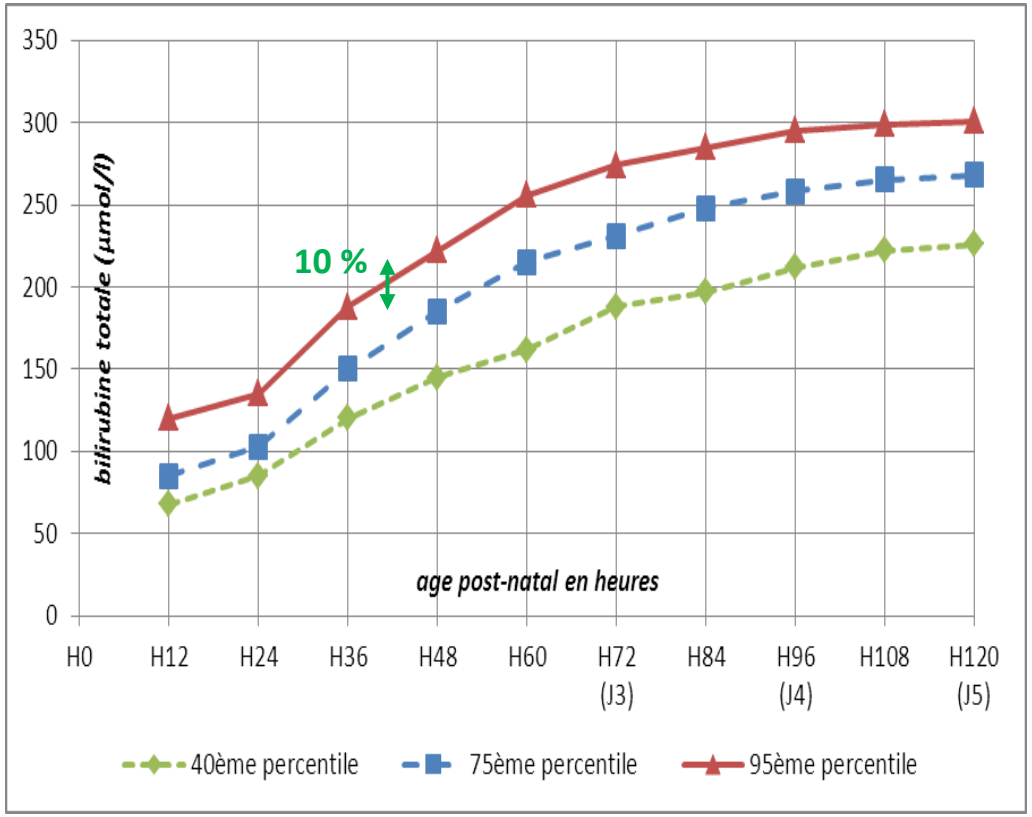
Clinical goal : prevention of severe hyperbilirubinemia

Cortey A et al. Management of jaundice in the newborn ≥ 35 GW: from screening to follow-after discharge. Guidelines for clinical practice – management and treatments after diagnosis. Recommendation SFN 2017 ; 24(2) : 192-203.

Bilirubin in neonates
Clinical Contexts (2)

- As in many countries, the French Society of Neonatology (SFN) has issued "Jaundice" recommendations incorporating:
  - ✓ Reference values of bilirubinemia: nomogram
  - ✓ Therapeutic indication curves (phototherapy and exchange transfusion) based on the total bilirubin (TSB) blood assay
  - ✓ Keys for the articulation in practice between TcB value (non-invasive quantification) and TSB value (invasive reference quantification) by blood measurement of total bilirubin.
- The therapeutic indications for jaundice (phototherapy and exchange transfusion) are based on the total bilirubin (BTS) blood assay, interpreted according to
  - ✓ gestational age,
  - ✓ postnatal age in hours and
  - ✓ conditions of vulnerability to bilirubin toxicity

BTS if TcB >75^{e}percentile or >250 µmol/L
Emergency if blinking or > 957 mep.



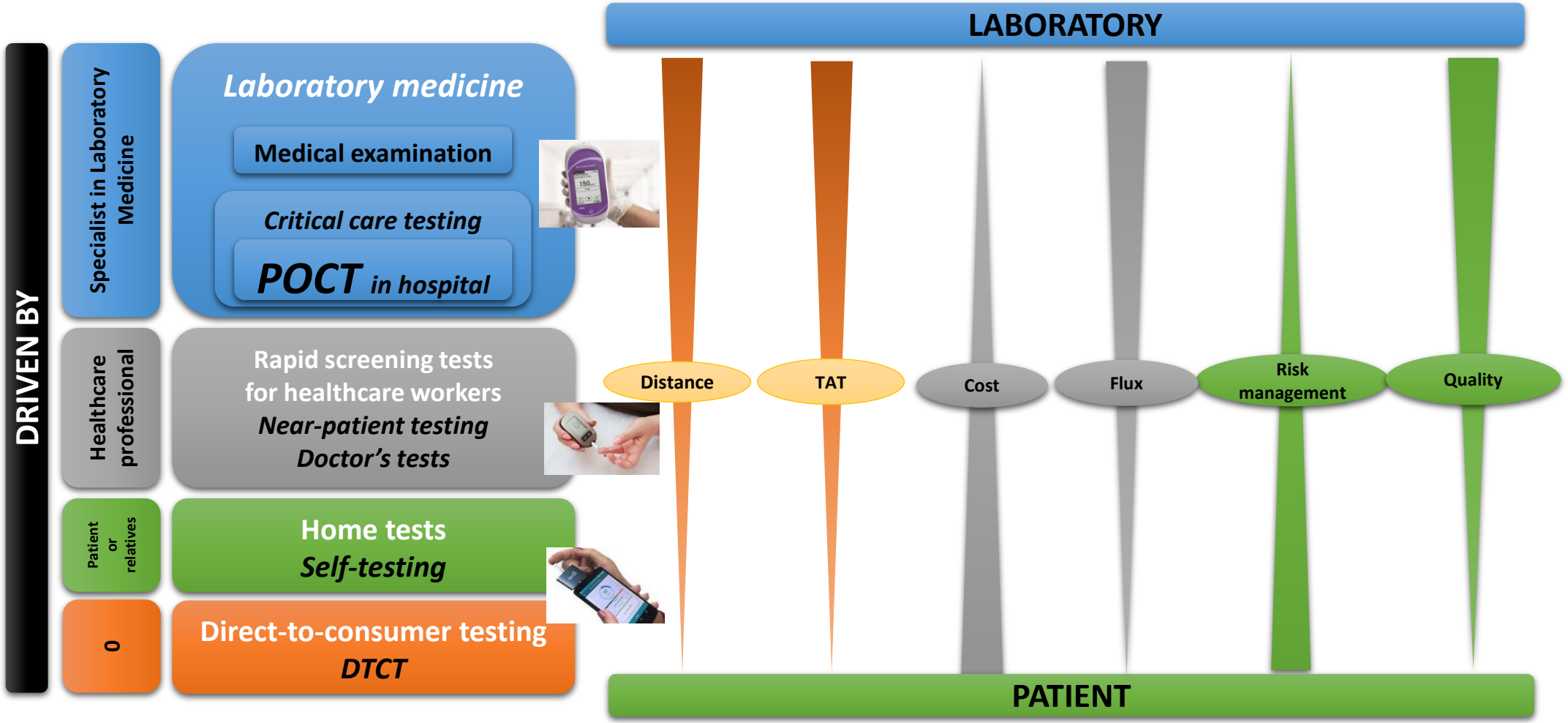
Bhutani VK, Johnson L: A proposal to prevent severe neonatal hyperbilirubinemia and kernicterus. J Perinatol. 2009 Feb;29 Suppl 1:S61-7

Cortey A.,Tourneux P., Bedu A., Renesme L., Raignoux J., Casper C., Truffert P. Management of jaundice in the newborn ≥ 35 GW: from screening to follow-after discharge Guidelines for clinical practice – management and treatments after diagnosis. Recommendation SFN 2015

American Academy of Pediatrics, Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation [published correction appears in Pediatrics. 2004;114:1138]. Pediatrics. 2004;114 :297 –316

Analytical goal: provide a reliable and accurate result (<10 % total error), even in POCT, for an optimized clinical decision

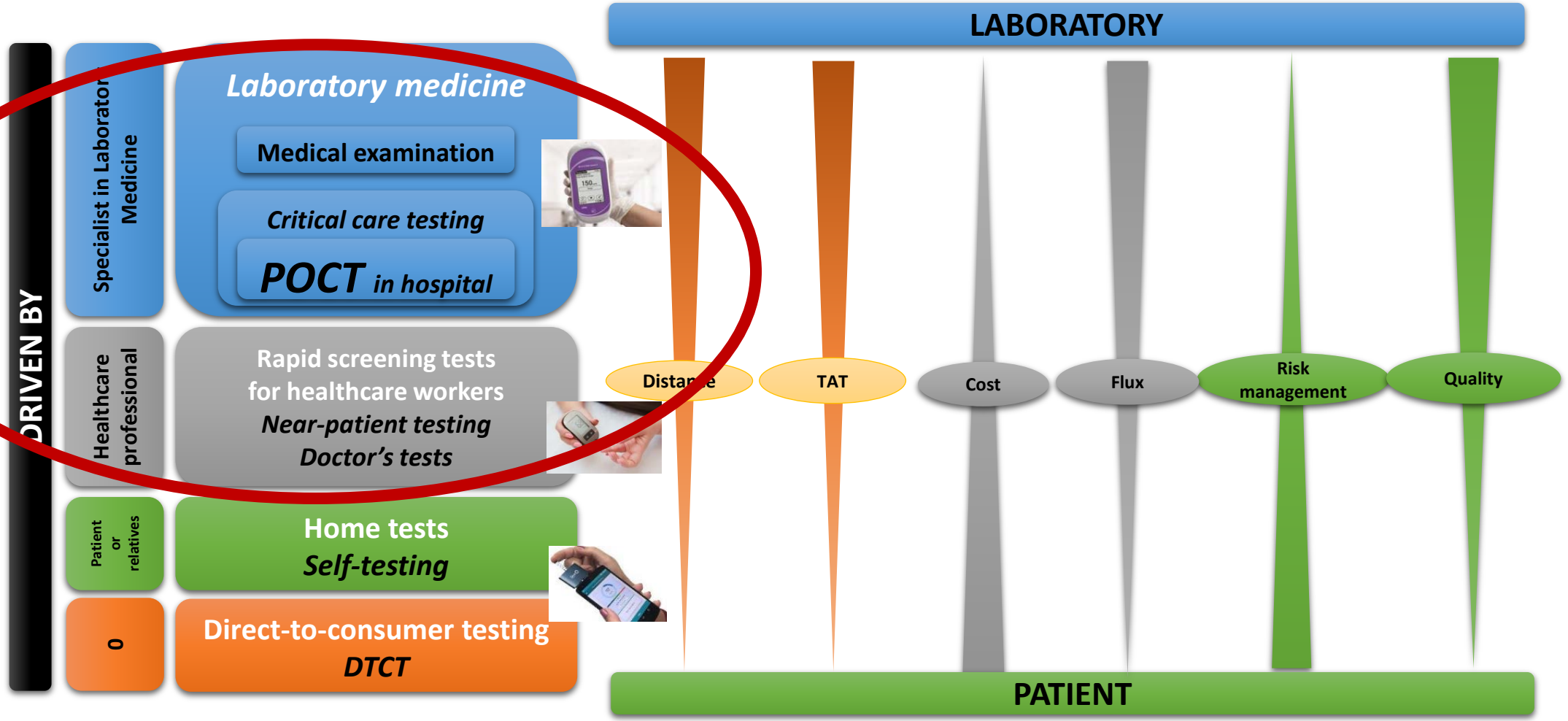
“Testing” outside clinical laboratory: a confusing continuum



4 situations: POCT, rapid screening tests, home tests and DTCT

“Testing” outside clinical laboratory: a confusing continuum

4 situations: POCT, rapid screening tests, home tests and DTCT



POCT for bilirubin in neonates is limited to tests driven by laboratory or by healthcare workers generally inside the hospital

Pyramid of clinical needs and neonatal bilirubinemia

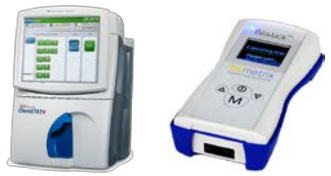
D km	TAT h
0	0
0,01	0,1
0,1	< 2
>1	< 6

Distance – Turn-Around Time

PATIENT

Transcutaneous bilirubinometer **TcB**
Screening tests devices*
Non invasive

POCT
POCT device**
Capillary or whole blood



Stat Lab
Stat analyzer
Serum or plasma

Clinical lab
Core lab analyzers
Serum or plasma

LABORATORY

*Screening tests: in France under supervision of healthcare professionals, not by lab

**POCT: in France under supervision of clinical lab

Utilisation clinique

Clinical unit - NICU

Transcutaneous test for the evaluation of bilirubinemia — **TROD**
- ✓ Screening
- ✓ Treatment Phototherapy
- ✓ Exit decision
- ✓ Post-release follow-up

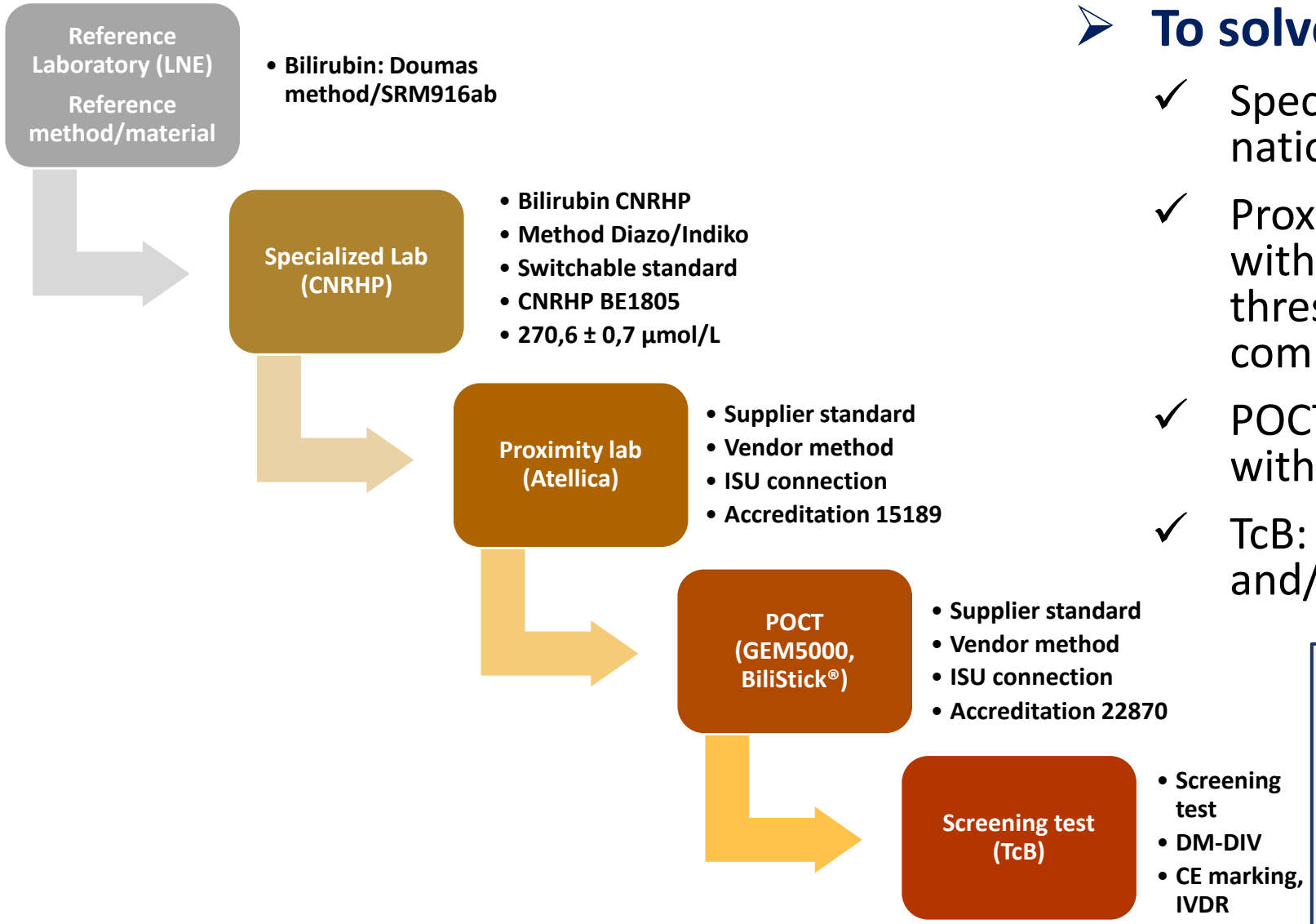
Confirmation of screening tests results by a lab result — **EBMD**
- ✓ Absence of displayed result of the Btc
- ✓ Early jaundice
- ✓ Btc value exceeding the 95th percentile of the nomogram

Laboratory

Confirmation of screening tests results by a lab result — **Examens Biologie**
- ✓ Absence of displayed result of the Btc
- ✓ Early jaundice
- ✓ Btc value exceeding the 95th percentile of the nomogram

Confirmation of screening tests results by a lab result
- ✓ Btc > 250 µmol/L
- ✓ Btc > 75 percentile of nomogram
- ✓ Btc with phototherapy indication value
- ✓ Discrepancy between visual assessment of jaundice and Btc
- ✓ Checking the effectiveness of phototherapy during the session and within 24 hours.

Laboratory needs and analytical challenges



➢ To solve at each level

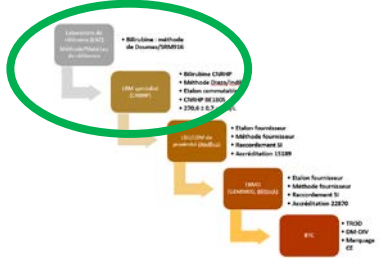
- ✓ Specialized labs: connection to the IS, national harmonization studies
- ✓ Proximity lab: choice of techniques, help with interpretation vs. consensual thresholds, inter-laboratory comparability monitoring (EQA/PT)
- ✓ POCT: same + comparability monitoring with the central lab
- ✓ TcB: help in choosing devices + lab and/or POCT results comparability

In response to these challenges, the CNRHP lab has carried out several local or national studies to progress towards better emergency interpretation of neonatal bilirubin results.

What to do at central lab level?

About standardization and harmonization of total serum bilirubin

CNRHP Study
Connection to International System of Units



STANDARDIZATION OF SERUM TOTAL BILIRUBIN MEASUREMENT FOR IMPROVED DIAGNOSIS AND MANAGEMENT OF NEONATAL JAUNDICE

Vincent DELATOUR[1], Michel VAUBOURDOLLE[2], Elisabeth LASNIER[2], Nathalie MARIO[2], Sophie BAILLEUL[2], Marie-Clotilde HAGUET[2] and Agnès MAILLOUX[3]

[1]LNE, [2]Services de Biochimie, HUEP, AP-HP, Paris, France, [3]CNRHP, Saint Antoine, AP-HP, Paris, France

Euromedlab – Athènes – Juin 2017

Identification d'un calibrant commutable pour réaliser une calibration *in silico*

ETALON BNL

Reference method value
Amount of substance concentration of bilirubin

Calibration laboratory	Reference laboratory II of the RfB
Material of investigation	Calibrator for bilirubin
Lot	BE1449
Manufacturer	Laboratoire national de métrologie et d'essais (LNE)
Customer	LNE
Method	Proposed IFCC reference method
Period of measurements	15.12.2014 to 18.12.2014

Code no. 1030

Analyte	Reference method value[1]	Uncertainty of measurement[2]	Number of accepted results
Bilirubin	287,4 µmol/L 16,80 mg/dL	6,3 µmol/L 0,37 mg/dL	4 Series on 2 Days
		2,2 %	12 Single values

One specimen was thawed on the first measurement day for series 1 and series 2.
One specimen was thawed on the second measurement day for series 3 and one for series 4.
[1] The reference method value is the mean of all single values of all measurement days

[2] The uncertainty of measurement is the combined expanded uncertainty.
The coverage factor is k = 2,0 Degrees of freedom: ν = >50
The uncertainty takes into account:
Standard error of the mean of the means
Standard uncertainty of the adjustment of the wavelength
Standard uncertainty of the spectrometric measurement
Standard uncertainty of the volume fraction of sample
Standard uncertainty due to the drift of the baseline
Standard uncertainty due to stray light
Standard uncertainty due to aging, evaporation and time measurements

The estimation of the uncertainty was performed according the "Guide to the Expression of Uncertainty in Measurement".

Note: The coefficient of variation (CV) of the combined single values is 1,0 %.

Hannover, 2014-12-18 Head of the calibration laboratory Person in charge

Dr. D. Grote-Koske R. Brasche/R. Klauke

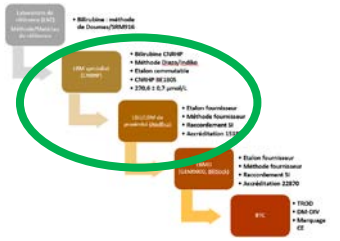
Laboratories	SAINT-ANTOINE Hospital
	Lab 1 : CNRHP
	Lab 2 : LBU
	Lab 3 : Biochemistry lab
	TROUSSEAU Hospital
	Lab 4 : Biochemistry lab
	TENON Hospital
	Lab 5 : Biochemistry lab
Analyzers	Indiko Thermo-scientific
	AU640 Beckman-Coulter
	DCX 800 Beckman-Coulter
	Architect ABBOTT
	Modular Roche
Methods	Method 1: Diazo Beckman / Indiko (Lab 1)
	Method 2 : Spectral / Indiko (Lab 1)
	Method 3 : Diazo Beckman / DXC 800 (Lab 2)
	Method 4 : Spectral /DXC 800 (Lab 2)
	Method 5 : Diazo / AU640 (labo3)
	Method 6 : Diazo Abbott / Architect (Lab 5)
	Method 7 : DPD / Roche Modular (Lab 4)
	Method 8 : Synermed / Roche Modular (Lab 4)

	BNLSEG	BNLAEG	HANL	HANH	PBQ
Method 1: Diazo Beckman / Indiko (Lab 1)	C	C	C	C	C
Method 2 : Spectral / Indiko (Lab 1)	NC	NC	C	C	NC
Method 3 : Diazo Beckman / DXC 800 (Lab 2)	C	NC	I	C	NC
Method 4 : Spectral /DXC 800 (Lab 2)	NC	C	C	NC	I
Method 5 : Diazo / AU640 (labo3)	C	C	C	C	NC
Method 6 : Diazo Abbott / Architect (Lab 5)	C	C	C	C	NC
Method 7 : DPD / Roche Modular (Lab 4)	C	C	C	C	NC
Method 8 : Synermed / Roche Modular (Lab 4)	C	C	C	C	NC

STANDARDIZATION OF SERUM TOTAL BILIRUBIN MEASUREMENT FOR IMPROVED DIAGNOSIS AND MANAGEMENT OF NEONATAL JAUNDICE
Vincent DELATOUR, Michel VAUBOURDOLLE, Elisabeth LASNIER, Nathalie MARIO, Sophie BAILLEUL, Marie-Clotilde HAGUE and Agnès MAILLOUX, EUROMEDLAB, Athènes Juin 2017

- **This study allowed to**
  - ✓ **Check the commutability** of a CNRHP BNL standard and an LNE HAN control material for 8 automaton/technical pairs (exception spectral method)
  - ✓ **Assign a value** to the CNRHP BNL standard by connection carried out by the LNE
- **And to be able to use**
  - ✓ **The CNRHP-BNL standard** for linking the total bilirubin assays carried out at the CNRHP and thus determining the expected values of Bilirubin during a harmonization study
  - ✓ **The switchable control samples** with assigned values

French National multicenter study CNRHP – SFBC – CNBH
Harmonization between French labs (1)



Synthèse

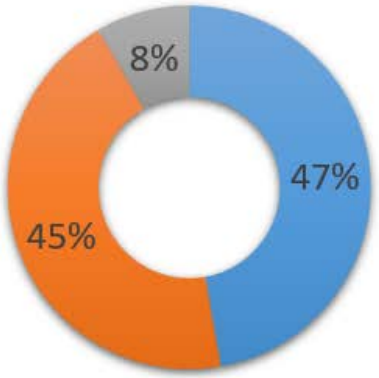
ANNALES DE BIOLOGIE CLINIQUE

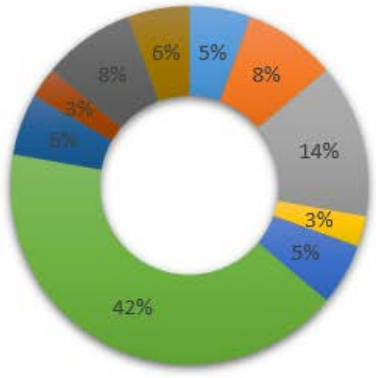
Ann Biol Clin 2020 ; 78 (4) : 383-97

Recommandations analytiques et cliniques pour l'utilisation de la bilirubinémie en néonatalogie

Analytical and clinical guidelines on neonatal bilirubinemia

Agnès Mailloux[1]
Anne Cortey[2]
Vincent Delatour[3]
Carole Poupon[4]
Michèle Rota[5]
François Schmitt[6]
Michel Vaubourdolle[7]
Groupe de travail
SFBC-CNBH-CNRHP
« Bilirubine néonatale »



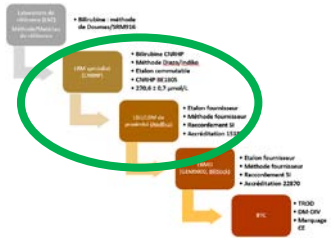


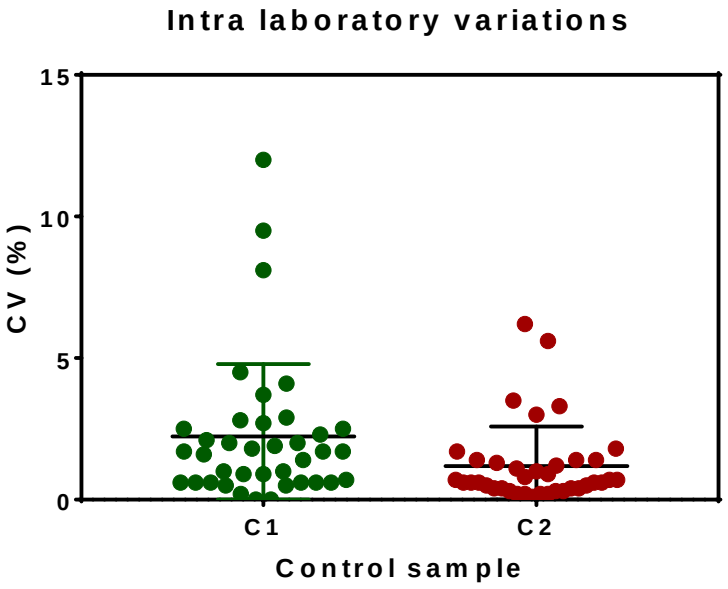
Laboratories repartition (n=36)

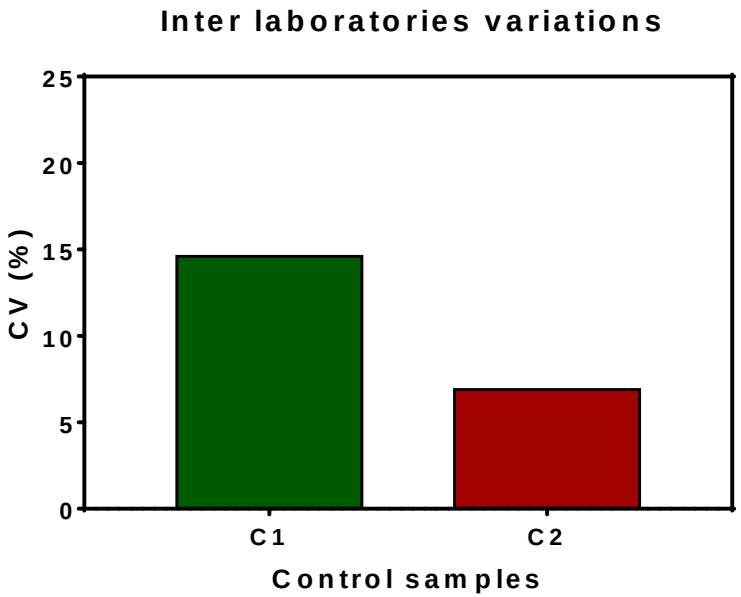
- **Hospitals representation 92%**
- **Presence of mainly-used analyzers in France**
- **Over representation of Roche analyzers**

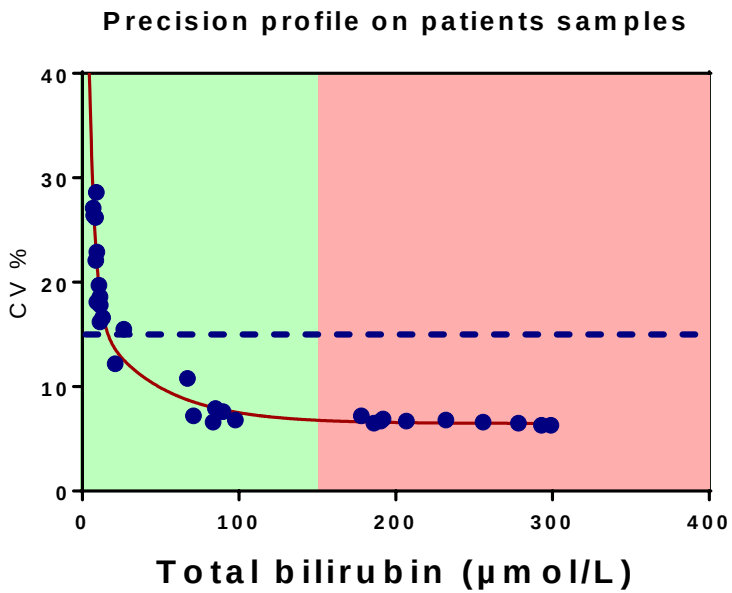
We had a representative sample of blood bilirubin measurement methods in France

French National multicenter study CNRHP – SFBC – CNBH
Harmonization between French labs (2) - fidelity





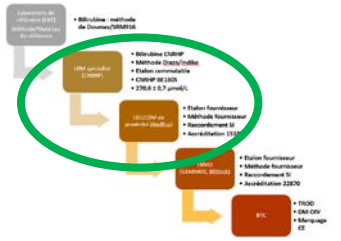




Intra and inter-laboratory variations on control and patient samples at decision thresholds (C2) in neonatology: globally acceptable

The methods most used in France by LBMs are precise in particular in areas of high values (>150 µmol/L) of clinical interest in neonatology

French National multicenter study CNRHP – SFBC – CNBH Harmonization between French labs (3) – Accuracy

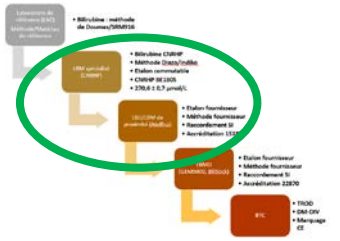


- **The methods used in France present significant inter-technical differences, linked to a drift in standardization over time (SRM916a).**

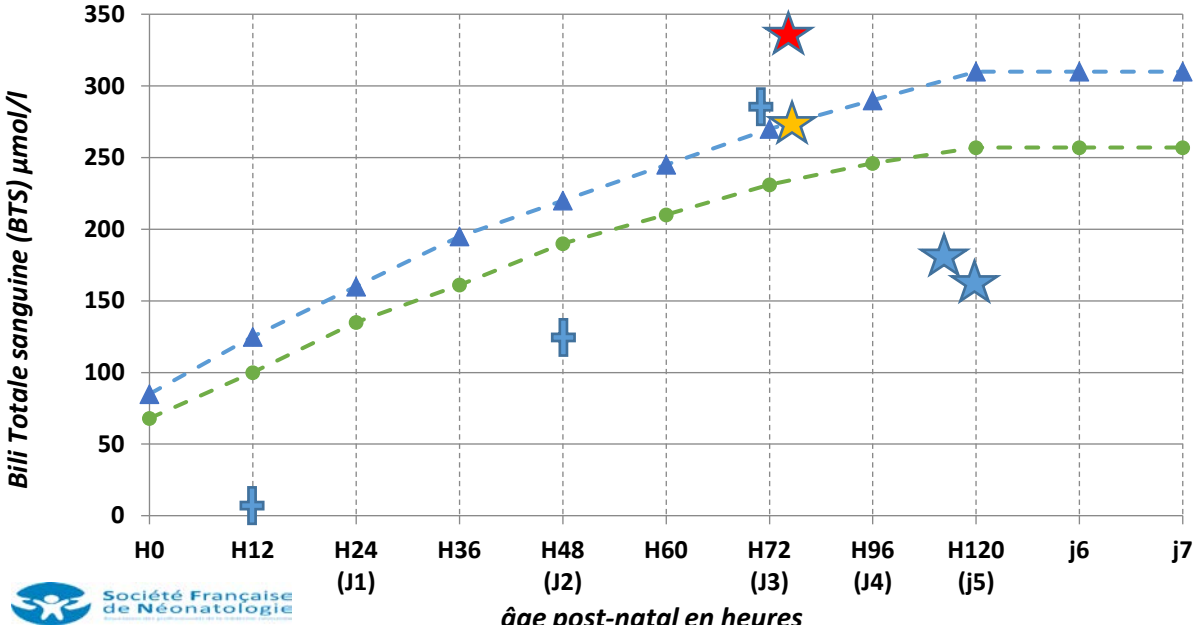
- **Above 150 µmol/L, differences from the expected values that can influence the clinical decision (>20%) are observed with:**
  - ✓ **Either an overestimation without major clinical impact: phototherapy initiated incorrectly or more quickly**
  - ✓ **Either an underestimation with the Roche method (the most widespread in France): possible clinical impact with possible delay in management**

IVD company	Analyzer	Relative bias for patients >150 µM
Abbott	Alinity	+ 10
	Architect	+ 20 (dispersion)
Beckman	AU	0
	DXc	+ 5
Ortho	Vitros TBIL	+ 30 (no clinical incidence)
	Vitros BuBc	- 10
Roche	Cobas	- 25 (clinical incidence but possible correction *in silico*
Siemens	Advia	+ 15
	Atellica	+ 20
	Vista	+ 5
ThermoFisher	Indiko	+ 10

French National multicenter study CNRHP – SFBC – CNBH Harmonization between French labs (4) – Clinical incidence



Born at 37 WA eutrophic vaginally from a first mother with blood group A RhD pos and RAI negative.
Good fit. Exclusive breastfeeding with difficulty getting started.
Weight loss at H72 12%
No early jaundice but severe jaundice at H72 with TcB at 270 µmol/l ✚ motivating TSB locally at 264 µmol/l ★ and at CNRHP at 302 µmol/l ★



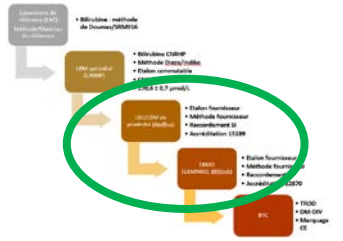
The clinical impact of an underestimation of serum bilirubin has been demonstrated in a case at Armand Trousseau Hospital. Requests for advice from the CNRHP confirmed that this type of situation occurs regularly in other centers. This analytical study of multicenter harmonization allowed

- ✓ **to better specify the nature and intensity of inter-technical variations for the measurement of total bilirubin concentrations in neonatology, depending on the techniques used**
- ✓ **to propose simple measures to correct the results when consequences on the clinical decision can occur with a direct application of the interpretation criteria recommended by the scientific societies (SFN)**

What to do at POCT level?

About clinic biological partnerships

Use of screening tests (TcB) and POCT bilirubin 2019 SFBC-CNBH-CNRHP Group survey

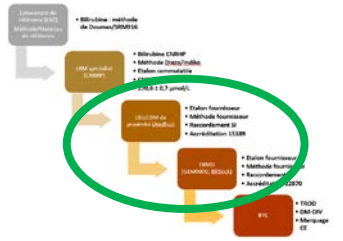


	Pratique majoritaire	Risk in neonatology
Transcutaneous bilirubin (TcB) Screening test	Knowledge by clinical lab specialists: ➢ Of the use of a TcB measurement device in their hospital: 30% ➢ Of the need for confirmation by the central lab of an alert value before a therapeutic decision: 20% ➢ Of the comparability of local TcB vs TB results: 10%	Incomplete management of results comparability between the different techniques with risk of erroneous interpretation in a critical situation Clinic biological partnership does not meet the clinical needs in neonatology
Whole blood Total Bilirubin POCT	➢ No device known 75% ➢ Implementation in project 3% ➢ Existing system for monitoring neonatology (work room, NICU, etc.) 16%	Clinic biological partnership does not meet the clinical needs in neonatology

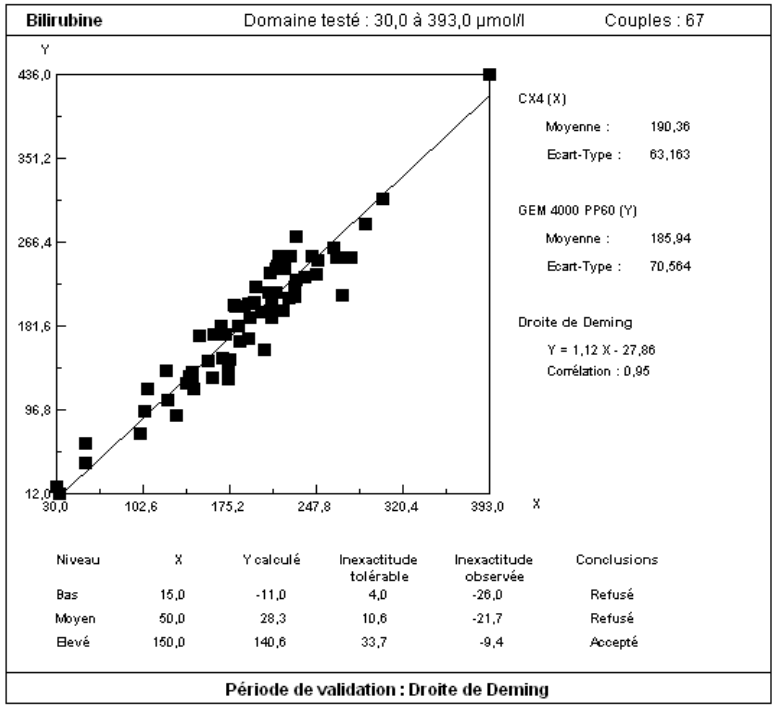
Some issues have been demonstrated

- ✓ **No continuity or coordination of neonatology practices between TcB, POCT (BT) and laboratory assays (BT)**
- ✓ **Confirmation of TcB before therapeutic decision not made or not known**
- ✓ **Btc-BT comparability not assessed with risk of misinterpretation of results**

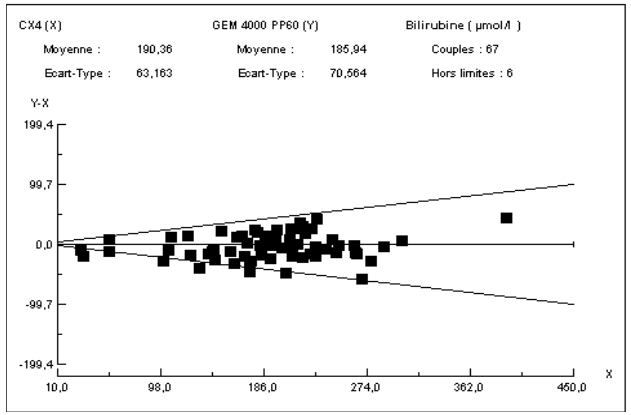
CNRHP study – Comparability POCT vs Central Lab
Use of the Werfen GEM 4000 CO-oximeter in Maternity



Total bilirubin assay using GEM Premier 4000: promising results for jaundice diagnosis in maternity wards, CPOCT, Boston 2010



Comparison study between bilirubin assay on the GEM 4000 and that carried out at the CNRHP by diazotization on Beckman CX4 CE (ISU connected method)



POCT BG/electrolytes devices that use CO-oximetry to measure bilirubin on whole blood are very precise and accurate and make it possible to obtain reliable values immediately in the delivery room.
They can be used both for the diagnosis of fetal hypoxia and for the confirmation of TcB

Performance

Very good precision
Very good comparability
Excellent practicability

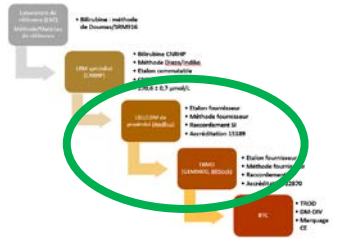
Quality

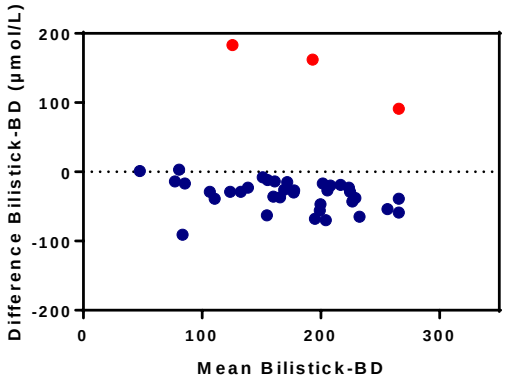
Efficient IT connection with identity monitoring and integrated quality assurance
Operator skills management
Accreditation 22870 – Risk management

Other advantages

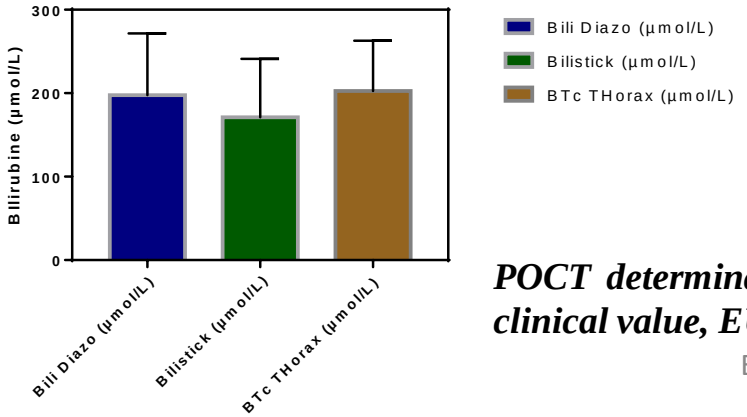
Mixed use with fetal hypoxia assessment (scalp + cord blood)

CNRHP study – Comparability POCT vs Central Lab
Use of BiliStick® on capillary blood





#	Bilistick	Reference	Bias	Bias%	Acceptable limit (%)	Conclusion
1	251	261	-10	-3,8	15	Accepted
2	156	184	-28	-15,2		Rejected
3	316	339,5	-23,5	-6,9		Accepted
4	171	184,5	-13,5	-7,3		Accepted
5	332	338	-6	-1,8		Accepted
6	253	260,7	-7,7	-3,0		Accepted
Mean	246,5	261,3	-14,8	-6,3		
SD	72,2	69,1	9,0	4,9		



- **Correct precision** in POCT context: CV<6% at 2 levels (200 and 270 µmol/L)
- **Comparability** POCT whole blood vs LBM plasma **globally acceptable** but average underestimation of 20 µmol/L vs expected lab value
- **Comparability** with TcB thorax: average underestimation of 20 µmol/L vs. TcB measured value. **BiliStick® cannot be used to confirm BTc**.
- **Significant interference of hemolysis** but good detection by the BiliStick® in 5 out of 6 cases. **Do not use BiliStick® in case of hemolysis**.
- **Risk management** by central lab difficult under ISO 22870 accreditation: no computer connection or operator management
- **Less efficient than a CO-Oximeter** integrated in a BG/Lytes analyzer
- **Interesting for centers that do not have either TcB or stat TSB**

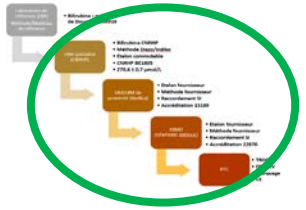
POCT determination of neonatal capillary bilirubinemia using BiliStick®: analytical performances and clinical value, EUROMEDLAB, MUNICH 2022

What to do for care optimization?

Using all emerging technologies

For an optimization of care

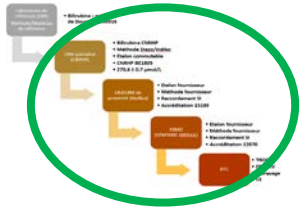
From the transcutaneous bilirubinometer to the laboratory via POCT devices

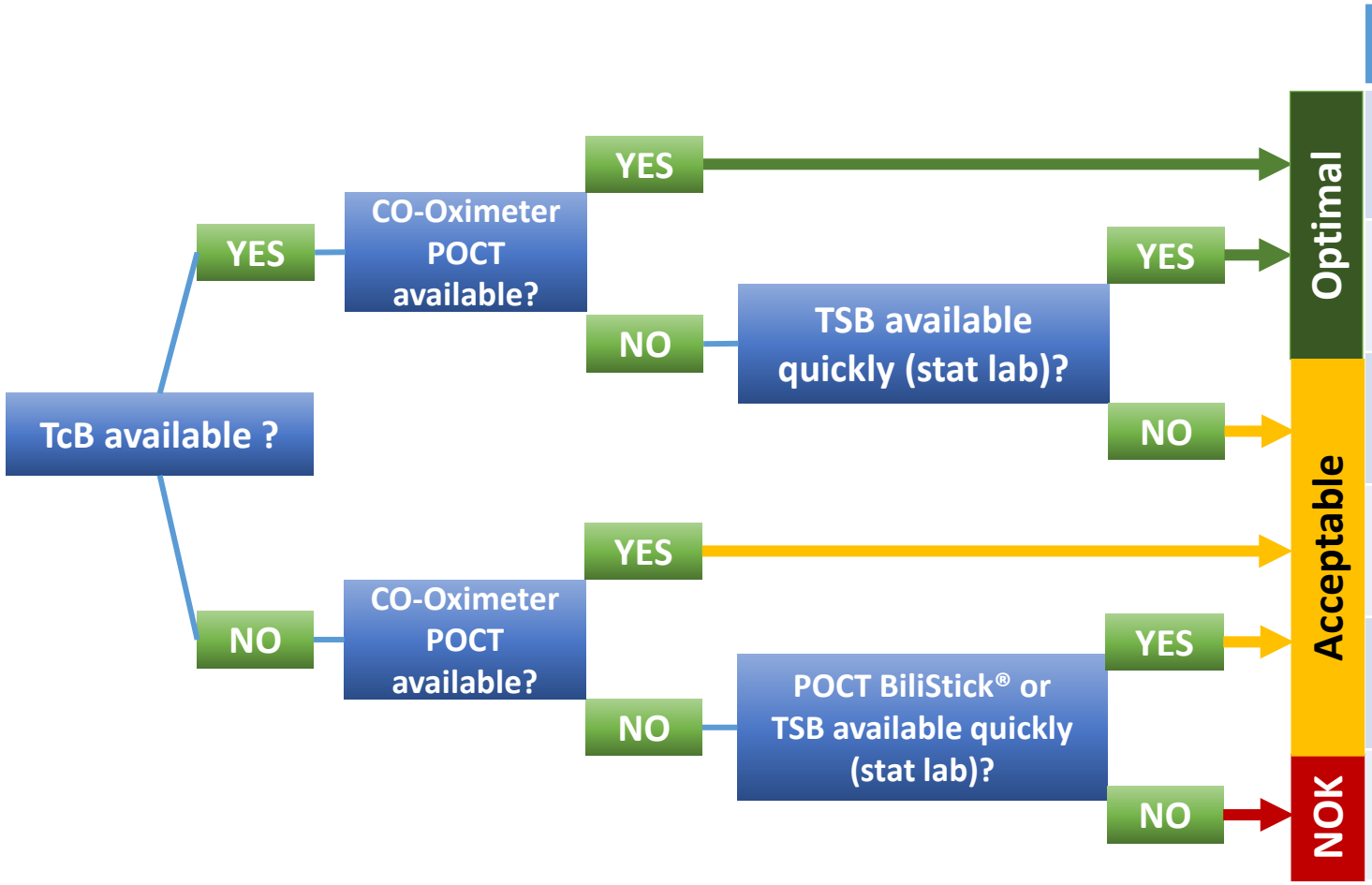


	Device	Advantages	Issues
Screening	Transcutaneous Bilirubinometers	Non invasive Results in real time	Heavy investment for a small structure
POCT	POCT CO-oximeter (GEM)	Minimally invasive – Reliable results Optimized risk management Mixed use for hypoxia management	Heavy investment for a small structure Implication of proximity lab on ISO22870 accreditation or risk management
POCT	Portable device for photometric measurement on capillary blood (BiliStick®)	Minimally invasive Usable if no TcB or POCT CO-oximeter	Underestimation of results No confirmation of TcB Hemolysis interference Adapt interpretation thresholds
Lab exam	Biochemistry stat analyzer	Reliable results Connection to ISU - harmonization Accreditation 15189 or risk management	Invasive (blood sampling) Logistics issues Inter-techniques differences Too long TAT for real-time follow-up

For an optimization of care

From the transcutaneous bilirubinometer to the laboratory via POCT devices





	Clinical Unit	Central Lab
Optimal	Autonomy Reliability OK – Non invasive Check TcB-POCT concordance	Check connection to ISU Follow POCT-Lab comparability POCT risk management
Optimal	Ensuring lab logistics Reliability OK – Non invasive Check concordance	Check lab connection to ISU Lab risk management (ISO 15189) Follow-up of stat tests TATs
Acceptable	Periodically check accuracy TcB vs. Central lab TSB Alert results confirmation	Check lab connection to ISU Lab risk management (ISO 15189) Follow-up comparability TcB-LabTSB
Acceptable	Autonomy Reliability OK Minimally invasive	Check lab connection to ISU Follow comparability POCT-Lab POCT risk management (ISO 22870)
Acceptable	Ensuring lab logistics Reliability OK – Invasive NO real-time follow-up	Check lab connection to ISU Lab risk management Follow-up of stat tests TATs
NOK	Clinical needs not taken into account	Insufficient biological response for follow-up in neonatology

Current and emerging technologies for the timely screening and diagnosis of neonatal jaundice

Mercy Thomas, Ronda F. Greaves, David G. Tingay, Tze Ping Loh, Vera Ignjatovic, Fiona Newall, Michelle Oeum, Mai Thi Chi Tran & Anushi E. Rajapaksa

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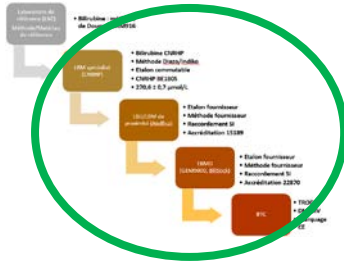
- **Ever-increasing need for a low-cost, simple to use screening technology to improve timely diagnosis and management of neonatal jaundice**
- **Review the literature, focusing on emerging technologies in the screening and diagnosing of neonatal jaundice**
- **Report on the challenges associated with the existing screening tools, followed by an overview of emerging sensors currently in pre-clinical development and the emerging POC devices in clinical trials to advance the screening of neonatal jaundice**
- **Benefits offered by emerging POC devices include their ease of use, low cost, and the accessibility of rapid response test results**
- **BUT further clinical trials are required to overcome the current limitations of the emerging POC's before their implementation in clinical settings**

The need for a simple to use, low-cost POC jaundice detection technology for newborns remains an unsolved challenge globally

Conclusions



- **Follow-up of neonatal jaundice important today**
  - ✓ Resurgence of jaundice + shortening of hospital LOS
  - ✓ Increased distance and time from core labs
  - ✓ Analytical discrepancies with risks of erroneous or delayed interpretation
- **Necessary efficient clinical-biological collaboration**
  - ✓ According to geographical and functional context, discussion to optimize the process of measuring neonatal bilirubin
  - ✓ Use the technological solutions available in Lab tests – POCT – Screening tests
  - ✓ Manage risks via an adapted QMS managed by the LBM

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