TREATMENT OPTIONS FOR HEMOPHILIA IN THE DEVELOPING WORLD

WFH-ISTH JOINT WEBINAR

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TREATMENT OPTIONS FOR HEMOPHILIA IN THE DEVELOPING WORLD

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AGENDA

1. Welcome
2. Introduction of speakers
3. Preventing of bleeds and arthropathy by prophylaxis in severe hemophilia
4. Challenges of diagnosis
5. Q & A
6. Summary

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SPEAKERS

- Prof Rolf Ljung is a pediatric hematologist from Malmo, Sweden
  - The country where the “prophylaxis” prevention of bleeds was invented for the treatment of hemophilia more than 50 years ago
- Prof Johnny Mahlangu is an adult hematologist from Johannesburg
  - Has been instrumental in introducing prophylaxis in South Africa
- Prof Sukesh Nair is Professor in the Christian Medical College Vellore
  - Is the Past Chair of the World Federation of Hemophilia (WFH) Laboratory Sciences Committee and the current Chair of the WFH IEQAS (International External Quality Assessment Scheme) Committee

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PROPHYLAXIS, LESSONS LEARNED FROM DECADES OF EXPERIENCE

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Lund University
Skåne University Hospital , Malmö

LUND UNIVERSITY

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AGENDA

1. Obstacles to the availability of prophylaxis
2. Primary prophylaxis – the Swedish model
3. Personalized prophylaxis
4. Low-dose primary prophylaxis

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OBSTACLES

There are two key obstacles to the global availability of prophylactic treatment:

Cost of treatment

Need for venous administration

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Primary prophylaxis – the Swedish model

- Start regular prophylaxis at the age of 1 year
  - 25 IU/kg/dose (=250 IU vial)
  - Avoid danger signals and intensive treatments during the first 20 ED (exposure days)
- Start once/week in a peripheral vein so child and parents get used to venipuncture – ***but*** – with the aim to reach 3/week or every 2nd day in hemophilia A and 2/week or every 3rd day in hemophilia B
- Port-A-Cath if intended frequency is not reached within a few months (approx. 30–35% need it)
- Educate parents, home treatment

Primary prophylaxis - the Swedish model

- At the age of 10–12, begin self-infusion
- At the age of 10–15, try to introduce daily prophylaxis in physically active children
- Continuous education of parents and children
- Allow most daily activities (even soccer on day of prophylaxis) to avoid social stigmatisation

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Ljung & Gretenkort Andersson. *Br J Haematol*. 2015;169(6):777-86; Oldenburg. *Blood*. 2015;125(13):2038-44

PERSONALISED/INDIVIDUALISED PROPHYLAXIS

Personalised prophylaxis should be the goal:

- Different approaches for hemophilia A and B?
- What is the aim of prophylaxis? Newly diagnosed child or elderly patient with target joints?
- Bleeding phenotype? ~15% bleed less
- Life style/physical activity?
- Susceptibility to arthropathy – subclinical/microbleeds?
- Individual pharmacokinetics (PK) vs vial sizes available
- Venous access?
- Compliance? – education and education !!
- Resources in the healthcare system

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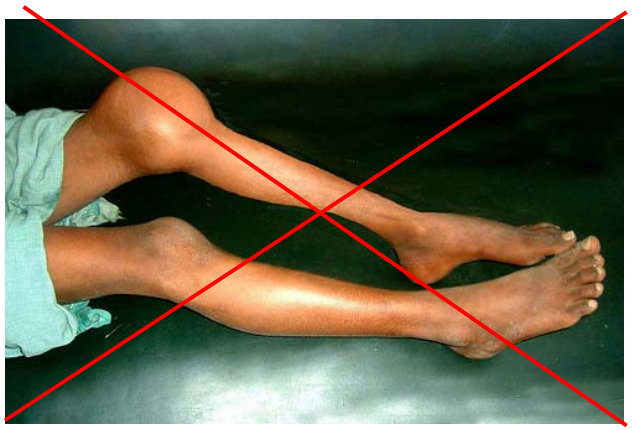
LOW-DOSE/ULTRA LOW-DOSE PRIMARY PROPHYLAXIS

Low-dose/ultra low-dose primary prophylaxis is a start-up option in countries with a restricted healthcare economy

- Low-dose prophylaxis (10-15/IU/kg/dose) will have a better outcome than 50/IU/kg/once weekly
- An extended half-life (EHL) product may be ideal for this purpose?!



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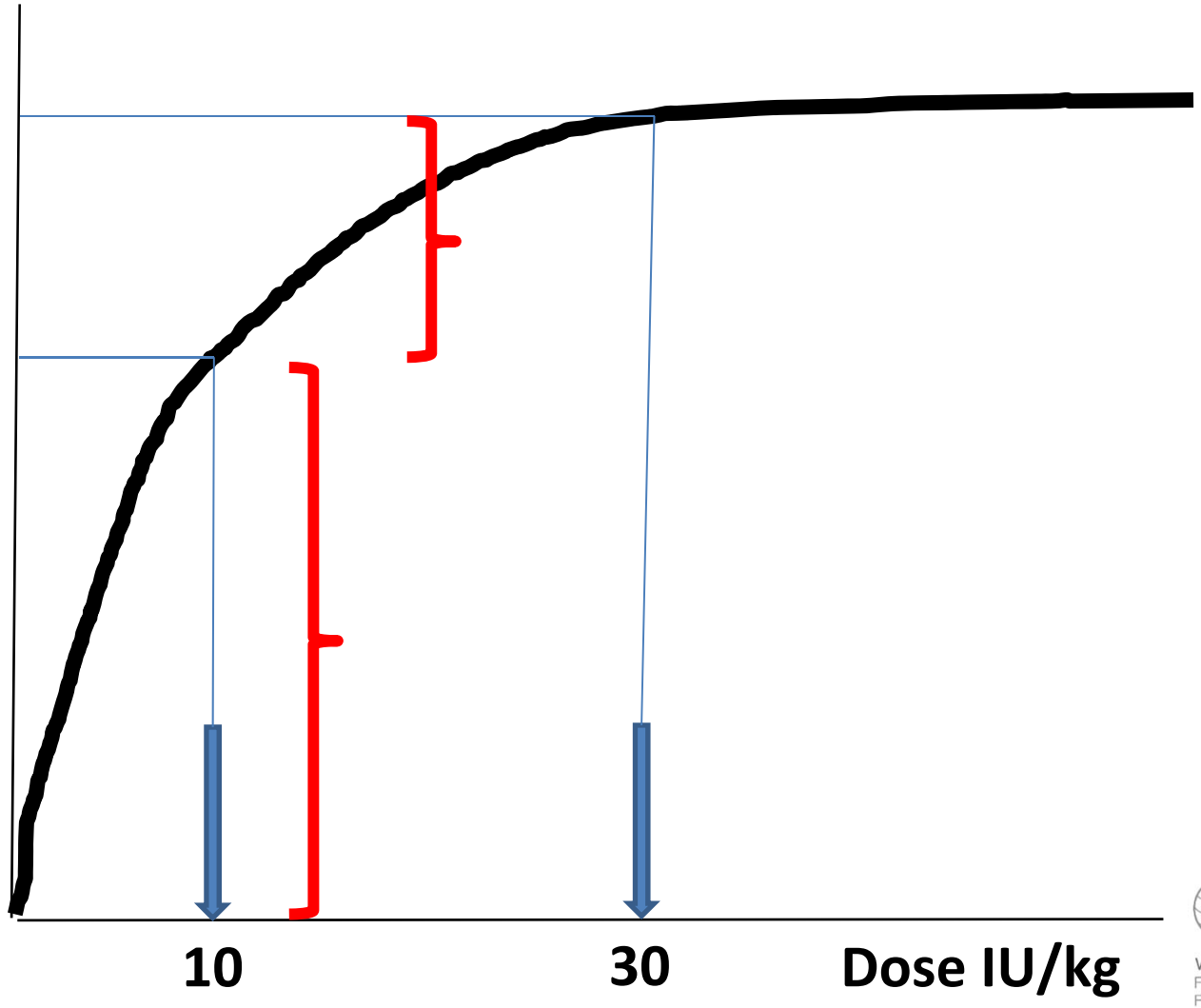
LOW-DOSE/ULTRA LOW-DOSE PRIMARY PROPHYLAXIS

Improvement shown by the reduction of bleeds



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PROPHYLAXIS FOR THE DEVELOPING WORLD: A DREAM OR POSSIBLE REALITY?

Johnny Mahlangu, MBBCh, MMed, FCPath
Professor/Director of Haemophilia Comprehensive Care Centre
University of the Witwatersrand, CMJAH and NHLS
Johannesburg, South Africa

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CONFLICT OF INTEREST DISCLOSURES

No conflict of interest to declare with regards to the content of this presentation.

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AGENDA

1. Benefits of and barriers to prophylaxis
2. Prophylaxis options for the developing world

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BENEFITS OF PRIMARY PROPHYLAXIS

- 83% reduction in number of bleeding episodes
- 66% improvement in joint function
- Less clinical and radiological deterioration of joints
- Fewer days lost from school/work
- 6-fold reduction in joint damage, by MRI
- 7-fold reduction in number of bleeding episodes/patient/year
- Increased physical activity
- Preserved BMD in the prophylaxis group

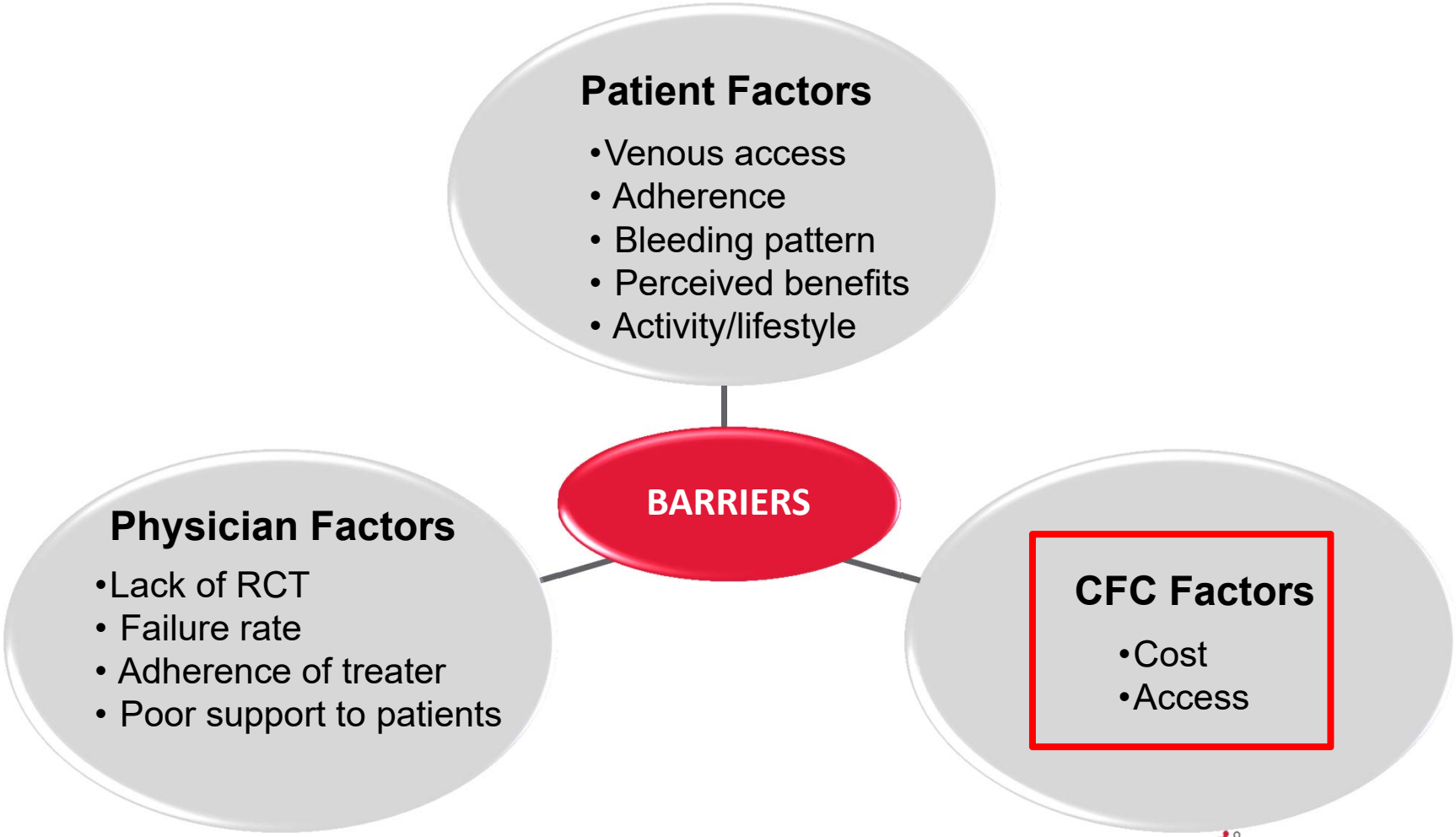
Wu et al, *Haemophilia*. 2011;17(1):70-4.

Aledort et al, *J Intern Med*. 1994;236(4):391-9.

Manco-Johnson et al, *N Engl J Med*. 2007;357(6):535-44.

Khawaji et al, *Haemophilia*. 2009;15(1):261-6.

BARRIERS TO PRIMARY PROPHYLAXIS



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Petrini. *Haemophilia*. 2007;13 Suppl 2:16-22.

COST BENEFIT RELATIONSHIP BETWEEN THERAPEUTIC GOALS AND STRATEGIES

Therapeutic goal	Therapeutic strategy
Enabling normal life	Primary prophylaxis
Enabling physical exercise	Long term secondary prophylaxis
Enabling normal ADL*	Regular secondary prophylaxis
Maintaining orthopaedic score	Irregular secondary prophylaxis
Preventing arthropathy	Frequent episodic treatment
Treating a bleeding episode	Infrequent episodic treatment

*ADL-activities of daily living

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COST DRIVERS IN PROPHYLAXIS

1. **Dose**
2. Dosing frequency

CLASSICAL APPROACH TO PROPHYLAXIS IN DEVELOPED WORLD

- Large doses: 25–50 IU/kg/dose
- Dosing frequency: 2–3 x / week FVIII
- Total yearly dose: 3500–8000 IU/kg/year
- National consumption: 5–10 IU / capita
- High Cost: 200–400 000 US$/patient/year

IS PROPHYLAXIS POSSIBLE IN DEVELOPING COUNTRIES?

Hypothetical country

- Total population — 50 million people
- People with hemophilia A — 5 000 people
- With severe hemophilia A — 3 000 people

	2014	2015	COUNTRIES REPORTING
Mean global per capita factor VIII usage	2.11 IU	2.28 IU	54
Median global per capita factor VIII usage	1.23 IU	1.04 IU	54
Interquartile range (IQR) global per capita factor VIII usage	3.57 IU (0.02 to 3.59)	3.86 IU (0.05 to 3.91)	54
Mean global per capita factor IX usage	0.35 IU	0.38 IU	47
Median global per capita factor IX usage	0.21 IU	0.21 IU	47
Interquartile range (IQR) global per capita factor IX usage	0.53 IU (0.005 to 0.53)	0.65 IU (0.009 to 0.66)	47

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WFH Annual Global Survey 2015, available at http://www.wfh.org/en/data-collection, accessed on December 1st, 2016.

IS PROPHYLAXIS POSSIBLE IN DEVELOPING COUNTRIES?

Hypothetical country

• Total population	50 million people
• People with haemophilia A	5000 people
• Severe haemophilia A	3000 people

At 1 IU/capita

• Total CFC	50 million IU
• Total CFC to sPWH (90%)	45 million IU
• Total CFC/PWH/yr	15 000 IU
• Total CFC/PWH/wk for 50wks/yr	300 IU/PWH/week
• For a child weighing 30 kg	10 IU/kg /week

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LOW-DOSE TREATMENT OF BLEEDS USING CLOTTING FACTOR CONCENTRATE

Study	Type of bleed	Therapeutic material	Dose (IU/kg)	Success rate (%)
Honig et al (1969)	Haemarthroses	FVIII concentrate	20 - 30	92
Britton et al (1974)	Haemarthroses	FVIII concentrate	10	97
Abildgaard (1975)	Haemarthroses	FVIII concentrate	10	96
Ashenhurst et al (1977)	Haemarthroses Other	FVIII concentrate	8 - 12	100
Penner and Kelly (1977)	Haemarthroses	FVIII concentrate	7 - 9 11 - 13 15 - 17	90 79 94
Weiss (1977)	Haemarthroses Other	FVIII concentrate	7·5 0 -12·5 12·5 - 20	89 94
Ripa et al (1978)	Haemarthroses	FVIII/FIX concentrate	3 - 7	100
Stirling and Prescott (1979)*	Haemarthroses	FVIII concentrate	5·7 3·0	85 71
Aronstam et al (1980)*	Haemarthroses (knee, severe)	FVIII concentrate	7 14 28	67 95 100
Aronstam et al (1981)	Haemarthroses	FVIII concentrate/others	11 - 16	78
Aronstam et al (1982)	Haemarthroses	FVIII concentrate	7 14	89 77

*Randomized trials.

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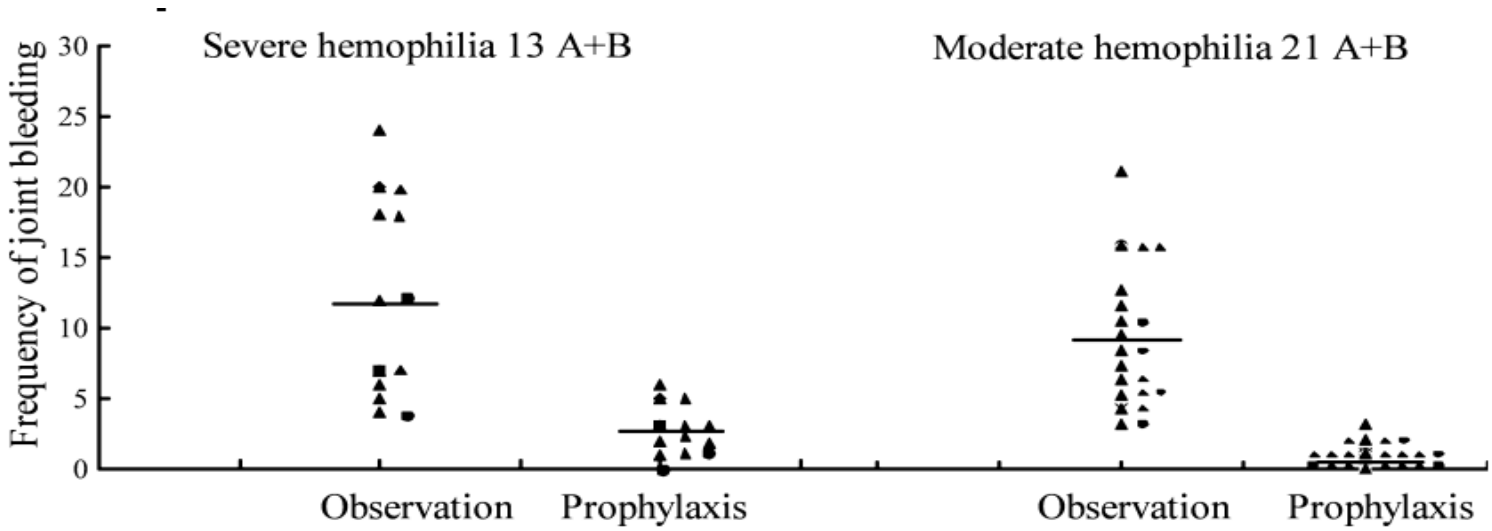
Srivastava. *Br J Haematol*. 2004;127(1):12-25.

REAL-WORLD EXPERIENCE OF LOW DOSE PROPHYLAXIS

Chinese experience - low dose 10 IU 2 x week
- secondary prophylaxis



Moroccan experience – low-dose primary experience

MUSFITH study - low dose is effective
- at high doses, the outcomes are less

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Wu et al, *Haemophilia*. 2011;17(1):70-4.

COST DRIVERS IN PROPHYLAXIS

1. Dose
2. **Dosing frequency**

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EFFICACY OF EHL-FIX PRODUCTS FOR PROPHYLAXIS IN ADOLESCENTS AND ADULTS

	rFIXFc[1]		rFIX-FP[2]		N9-GP[3]	
Dosing frequency (days)	q7 days/	q10 days	q7 days/	q14 days	q7 days/	q7 days
ABR, median (IQR)	3.0 (1.0, 4.4)	1.4 (0.0, 3.4)	0.0 (0.0, 1.87)	1.08 (0.0,2.7)	2.93 (0.9,6.0)	1.0 (0.0, 4.0)

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Powell et al, *N Engl J Med*. 2013; 369(24):2313-23; Santagostino et al, *Blood*. 2016;127(14):1761-9; Young et al, *Thromb Res*. 2016;141:69-76.

SUMMARY

- Yes, prophylaxis in the developing world is not just a dream, it is a reality we can all implement
- Prophylaxis is achievable through a dual approach of:
  - Reducing the dose of CFC and/or
  - Reducing the dosing frequency using extended half-life products
- This approach will reduce the biggest barrier to prophylaxis which is cost whilst achieving the desired beneficial outcomes of prophylaxis practice

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LABORATORY DIAGNOSIS OF BLEEDING DISORDERS: CHALLENGES IN THE DEVELOPING WORLD

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Vellore, India

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AGENDA

1. Minimal requirements for laboratory diagnosis of a patient with increased bleeding tendency
2. Challenges to its implementation
3. Strategies to overcome these challenges

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MINIMAL REQUIREMENTS FOR LABORATORY DIAGNOSIS OF BLEEDING DISORDER

A simple algorithmic approach following an abnormal screening test (PT/APTT):

1. Identification of a factor deficiency or inhibitor
2. Confirmation by assay
3. Checking the accuracy of these procedures by participation in an EQAS (external quality assessment scheme) such as WFH-IEQAS

IDENTIFYING THE CHALLENGES – DATA FROM WFH-IEQAS

- Sourced from an accredited PT provider – UKNEQAS, Sheffield
- Participants are mostly Hemophilia Treatment Centres (HTCs) in major cities
- WFH pays for participation of 94 laboratories (data from the 38th survey just completed)

Region		# Participants	
Asia	Middle East and South Asia	15	39
	China	8	
	South East Asia	16	
Africa			17
East Europe			18
America	South America	8	20
	Central America and Caribbean	12	

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Courtesy of Ian Jennings, UKNEQAS.

IDENTIFYING THE CHALLENGES– NON RETURNS FOR SCREENING TESTS

Region			#	Non return
Asia	ME and SA	5/15	39	7
	China	0/8		
	SEA	2/16		
Africa			17	4
East Europe			18	4
America	SA	3/8	20	7
	CA and Carib	4/12		

- No reagents available
  - Available earlier, have been exhausted
  - Not purchased
    - No funds provided for these reagents
  - Not supplied
- One participant had issues with skilled personnel

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Courtesy of Ian Jennings, UKNEQAS.

NON RETURNS FOR FVIII:C ASSAY – INADEQUACIES IN REAGENT PROCUREMENT

Summary of FVIII:C Participation in WFH-IEQAS						
Region			#: 91	Non return: 38		
Asia	ME and SA	15	38	6/15	14	14 outliers and 9 persistent outliers
	China	8		3/8		
	SEA	15		5/15		
Africa			16		7	
East Europe			18		7	
America	SA	8	19	4/8	10	
	CA and Carib	11		6/11		

- 23/53 outliers
- WFH provides support for troubleshooting these outliers
  - Visit to the laboratory by an expert who volunteers for WFH
  - Through e-mail connection with an expert

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Courtesy of Steve Kitchens, UKNEQAS.

WFH SUPPORT FOR POORLY PERFORMING LABORATORIES

- A major hospital that is an HTC (Hemophilia Treatment Centre)
- Its laboratory had a letter from WFH-IEQAS about persistent significant outliers for FVIII assay
- Forwarded to a Laboratory Sciences Committee member of WFH in that region for corrective action

Participant No: XX

Test	**FVIII:C**
Sample no.	**W09:14**
Your Method	**I stage factor assay**
Your normal range (u/dl)	50.0 – 150.0
Your result (u/dl)	**44.0**
UK NEQAS Meadian Result	**29.3**
Your grade*	D
Your grade for the last 3 surveys*	Persistent Outwith consensus
Your cumulative performance 3 surveys	**D/D/E**
Your interpretation	**Abnormal**
UK NEQAS programme interpretations(%) Normal Borderline Abnormal	 1.9 0.5 97.6

Participant No: 21

Test	**FVIII:C**	**FIX:C**
Sample no.	**W09:14**	**W09:15**
Your Method	**1 stage factor assay**	**1 stage factor assay**
Your normal range (u/dl)	50.0 - 150.0	50.0 - 150.0
Your result (u/dl)	**29.3**	**132.3**
UK NEQAS Median Result (u/dl)	**29.3**	**129.0**
Your grade*	a	A
Your grades for the last 3 surveys*	B/C/a	A/d/A
Your cumulative performance (3 surveys)*	Within consensus	Within consensus
Your interpretation	**Abnormal**	**Normal**
UK NEQAS programme interpretations (%) Normal Borderline Abnormal	 1.9 0.5 97.6	 90.7 1.2 8.1

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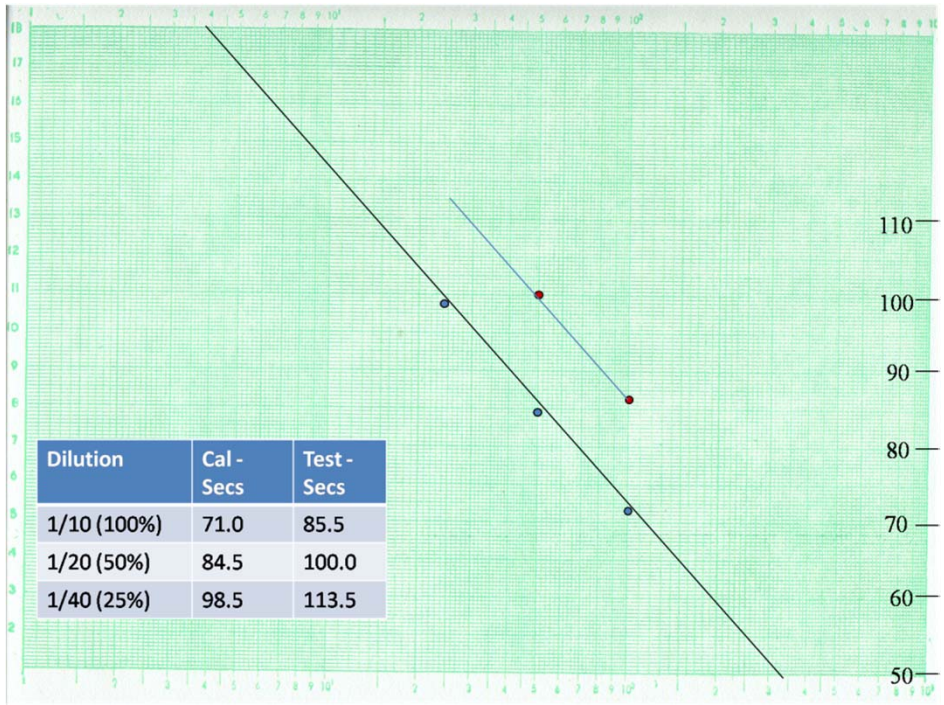
Courtesy of Steve Kitchens, UKNEQAS.

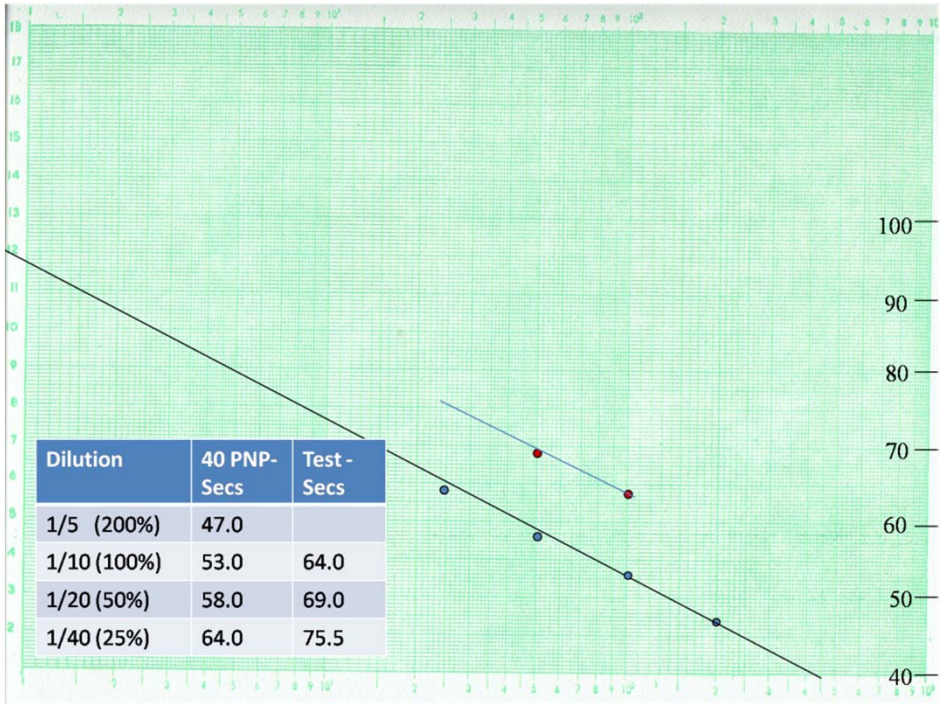
IDENTIFYING THE CHALLENGES – DETERIORATION OF REAGENTS



Dilution	Cal - Secs	Test - Secs
1/10 (100%)	71.0	85.5
1/20 (50%)	84.5	100.0
1/40 (25%)	98.5	113.5

100% (1/10 dilution) timings very high

FVIII in the calibrator has deteriorated



Dilution	40 PNP- Secs	Test - Secs
1/5 (200%)	47.0	
1/10 (100%)	53.0	64.0
1/20 (50%)	58.0	69.0
1/40 (25%)	64.0	75.5

Difference of timings between dilutions higher

FVIII-deficient plasma has deteriorated

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PREPARING FVIII-DEFICIENT AND REFERENCE PLASMA IN-HOUSE

- If FVIII–deficient plasma and pooled normal plasma cannot be obtained from a reliable commercial source, it may be possible to prepare it locally
- FVIII-deficient plasma may be obtained from a consenting patient with severe hemophilia provided it:
  - Completely lacks FVIII (<1 IU/dl, <0.01 IU/ml)
  - Does not contain any inhibitor
  - Contains normal concentrations of von Willebrand factor (VWF) and all the other clotting factors
  - Is negative for viral markers
- Pooled normal plasma (PNP) may be obtained from consenting “normal” individuals, keeping in mind the following:
  - Ideally, the concentrations of FVIII or FIX in the resulting pooled plasma are close to 100 IU/dl and should, ideally, be calibrated in international units (IU)
  - This can usually be achieved by pooling plasma from 20 individuals (requires a lot of effort, but is worth it if aliquots of the resulting pool can be stored appropriately):
    - –80°C for up to 1 year
    - –20°C for up to 1 month (freezer must not have autodefrost cycle)

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POOLED NORMAL PLASMA VS SMALL PNP

Source	FVIII:C	FIX
40 PNP	107.9	104.0
5 PNP	119.8	115.0
3 PNP - a	111.8	104.6
3 PNP - b	111.8	115.4

EVALUATING REAGENTS PREPARED IN-HOUSE – EASY SOLUTIONS FOR LABORATORIES THAT HAVE PROBLEMS WITH POOR REAGENTS OR NO REAGENTS

- Those laboratories who are non-returners for FVIII:C but return results for APTT can make the reagents they need in-house
- The clotting time for each mixture in the assay is determined by the quality of its contents and the concentrations of the factors
- Verify a few typical results to evaluate whether the reagents are behaving as they should in the assay:
  - A 1:10 dilution of the pooled normal plasma with FVIII-deficient plasma typically gives a clotting time of 52–65 seconds
  - The clotting times of a series of dilutions (such as 1:10 vs 1:20; 1:20 vs 1:40) typically differ by 5–9 seconds

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IDENTIFYING THE CHALLENGES – INADEQUACIES IN ALGORITHMIC APPROACH: MIXING STUDIES FOR FACTOR DEFICIENCY OR INHIBITOR

Diagnostic challenge:

- Sample is from a 10-year-old male child with a history of bleeding into joints and H\O transfusions
- PT: 11.1 s (normal reference range 10–12 s)
- APTT: 60.0 s (normal reference range 25–35 s)

Sample WS2013	n
Total Returning Results	36
Total Returning Overall Interpretations	25
Severe Hemophilia A	15
FVIII Deficiency/Hemophilia A	6
Hemophilia or VWD (no VWF assay available)	1
Moderate Hemophilia A	2
Moderate Hemophilia A + latent Hemophilia B	1
APTT 1:1 npp immediate mix	15
APTT incubated mix/inhibitor screen	3

Courtesy of Ian Jennings, UKNEQAS.

LABORATORY PERSONNEL TRAINING – OVERCOMING LIMITATIONS IN PERSONNEL AND PROCEDURES

Harmonization

- WFH and ISTH joint Training-the-Trainers workshops
- ISTH and WFH Fellowships to expert centres
  - IHTC (international hemophilia training centers)
- WFH Twinning – developing centre with an expert centre
  - Equipment/coagulometers
  - Start-up reagents
- Enrollment in an accredited PT (proficiency testing)/EQAS program – sponsored by WFH

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LIMITATIONS

Inadequacies in trained personnel

Inadequacies in procedures – mixing studies

- Significance of missing an inhibitor on/for prophylaxis

Inadequacies in sustaining a coagulation laboratory

- Low sample numbers (low referrals due to lack of awareness among medical personnel)
- Short shelf-life of reagents, high cost of reagents and consumables

Inadequacies from some manufacturers

- Availability of quality reagents
- Priority listing – low (esp. when funds are low)

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HEMORRHAGIC DISORDER MANAGEMENT

Coagulopathy

- Post-partum hemorrhage (PPH), viral hemorrhagic fever, trauma

Same tests required (APTT/FVIII:C/fibrinogen)

- Essential for management – helps determine blood component to be transfused

Blood component manufacturing, well-developed in developing world, but:

- No tests to ensure quality of blood components
- No tests to ensure quality of FVIII and fibrinogen in cryoprecipitate and fresh frozen plasma

Develop coagulation laboratory in transfusion services

- Ensures sustenance of coagulation laboratory services
- Benefits the bleeding disorder community

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RECOMMENDATIONS

1. Increasing awareness of laboratory management of hemorrhagic and bleeding disorders through seminars, workshops, and advocacy
2. Implementation of rational use of blood components and graded establishment of laboratory tests (followed by enrollment in an EQAS program)
3. Simple to perform and reproducible laboratory tests need to be developed (in-house methods)
4. Programs of the ISTH/WFH in training laboratory personnel will help achieve this goal

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CONCLUSIONS

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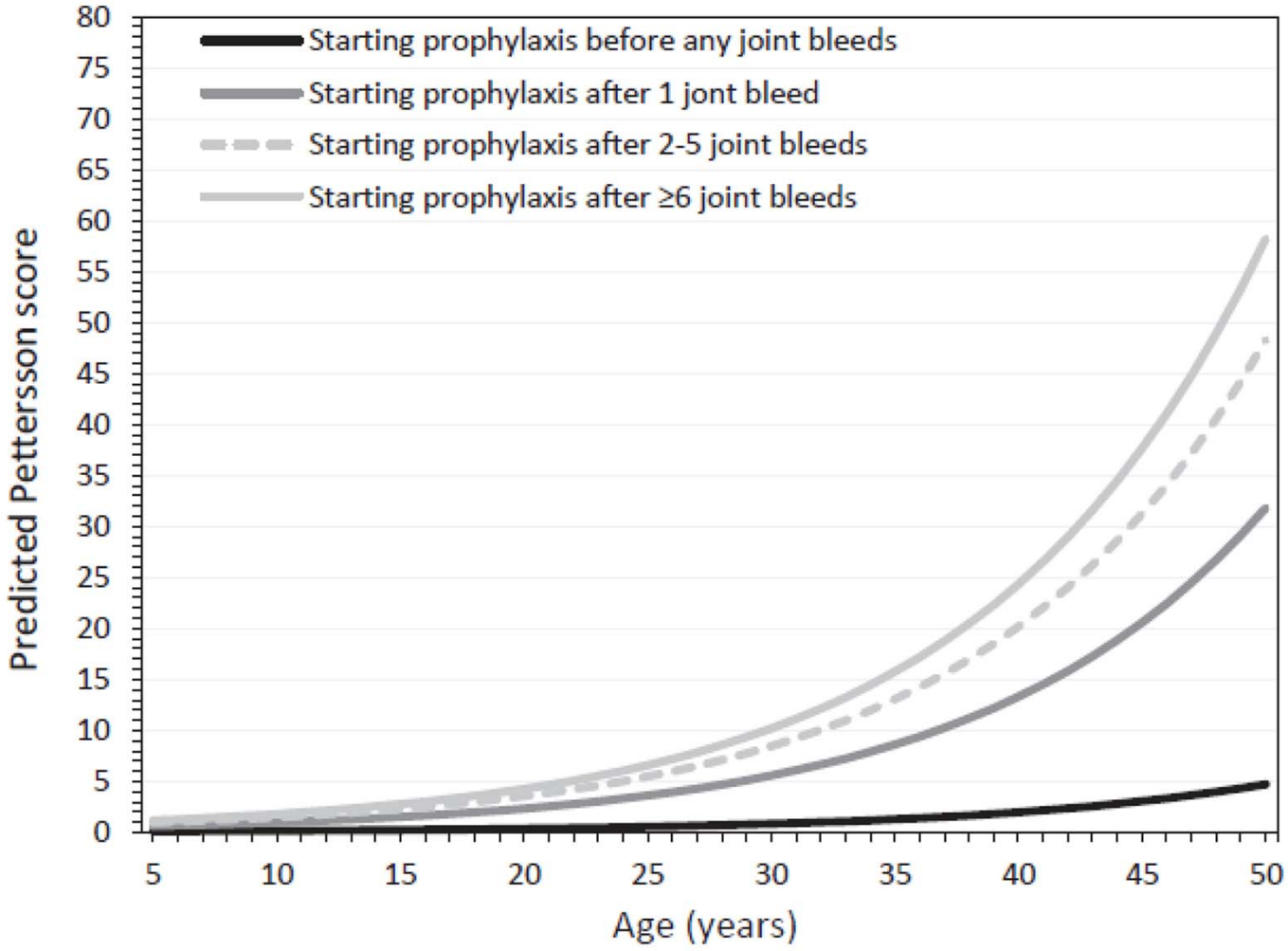
CONCLUSIONS

- Prophylaxis is the preferred treatment for all people with severe hemophilia
- On-demand treatment is only for acute bleeds
- To prevent arthropathy, prophylaxis needs to be started early, before 3 years of age

CONCLUSIONS



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Nijdam et al, *Haematologica*. 2015 Mar;100(3):e84-6

THANK YOU

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