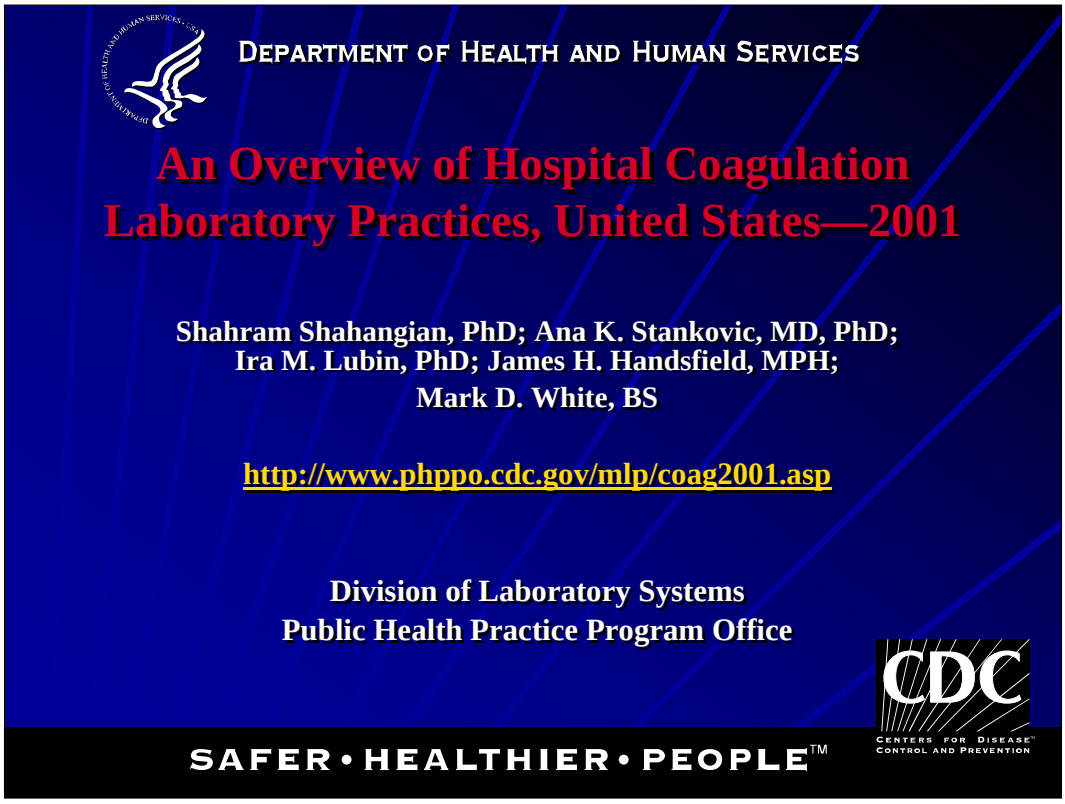
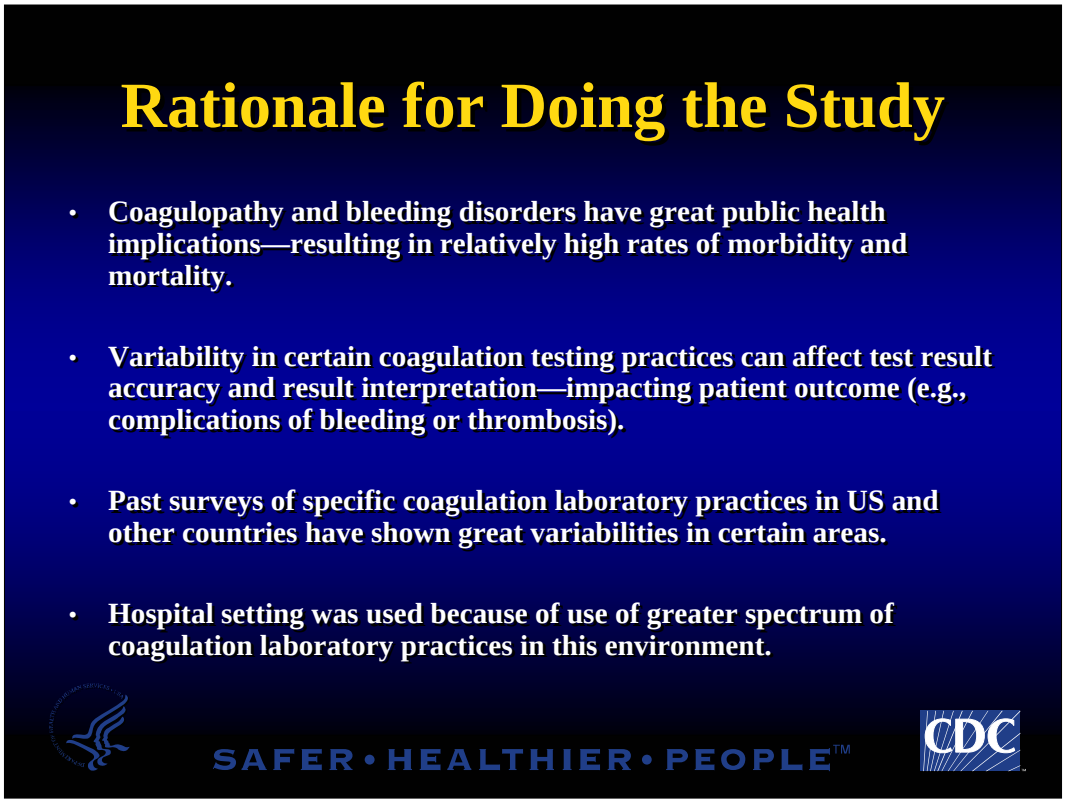


I would like to present to you today some of our findings in a survey of US hospitals' coagulation laboratory practices. This study was conducted in 2001, and it involved 800 hospitals.

Also, you can download the full text of the report in either PDF or HTML at this URL.



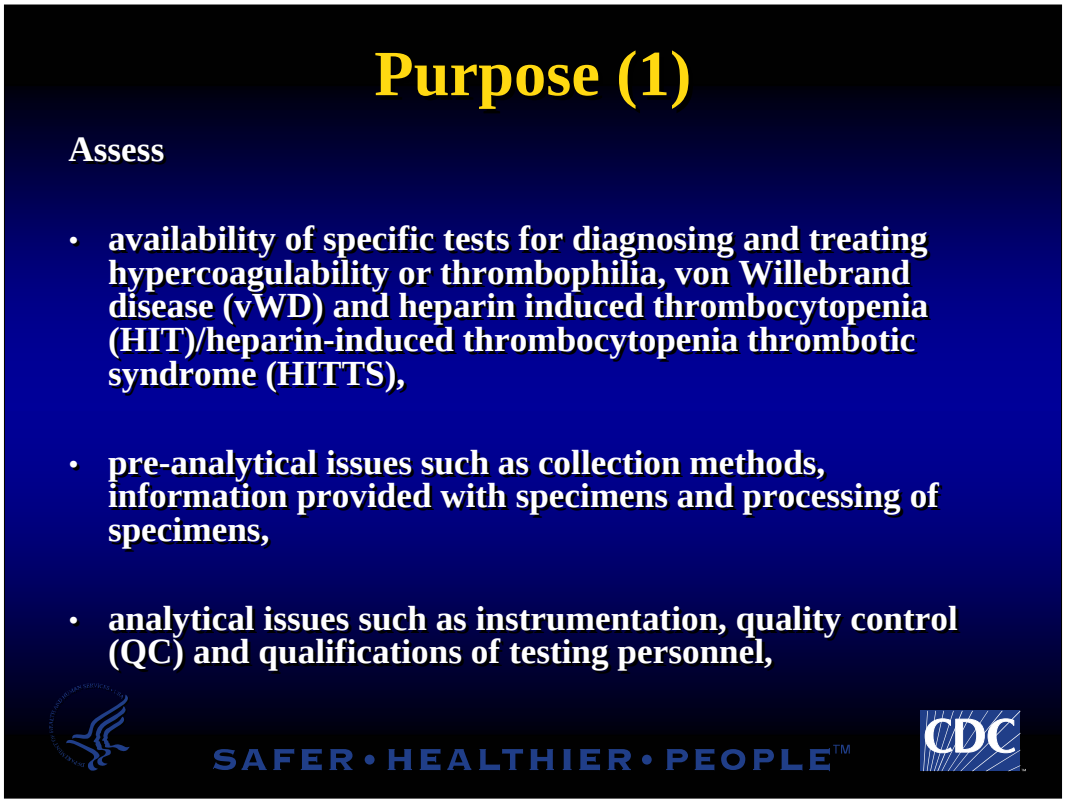
We set out to carry out this study because

•coagulation and bleeding problems have great societal burden of suffering;

•variation in some testing practices impact result accuracy and interpretation, and patient outcome; and

•previous studies have demonstrated great variabilities in certain consequential practices.

We used hospitals as the testing environment to address a broader spectrum of testing practices that are not amenable to observation in usual office laboratories.



The purpose of this study was to

•evaluate availability of tests for workup of hypercoagulability, von Willebrand disease and heparin induced thrombocytopenia/thrombotic syndrome;

•assess various pre-analytical and analytical stages of the testing process; …

Purpose (2)

Assess

- **post-analytical issues such as result reporting, interpretations and recommendations, and**
- **use of selected laboratory practices specific to each test that are subject to variation (such as availability, methodology and sensitivity) and that are critical to the diagnostic or therapeutic use of the test.**

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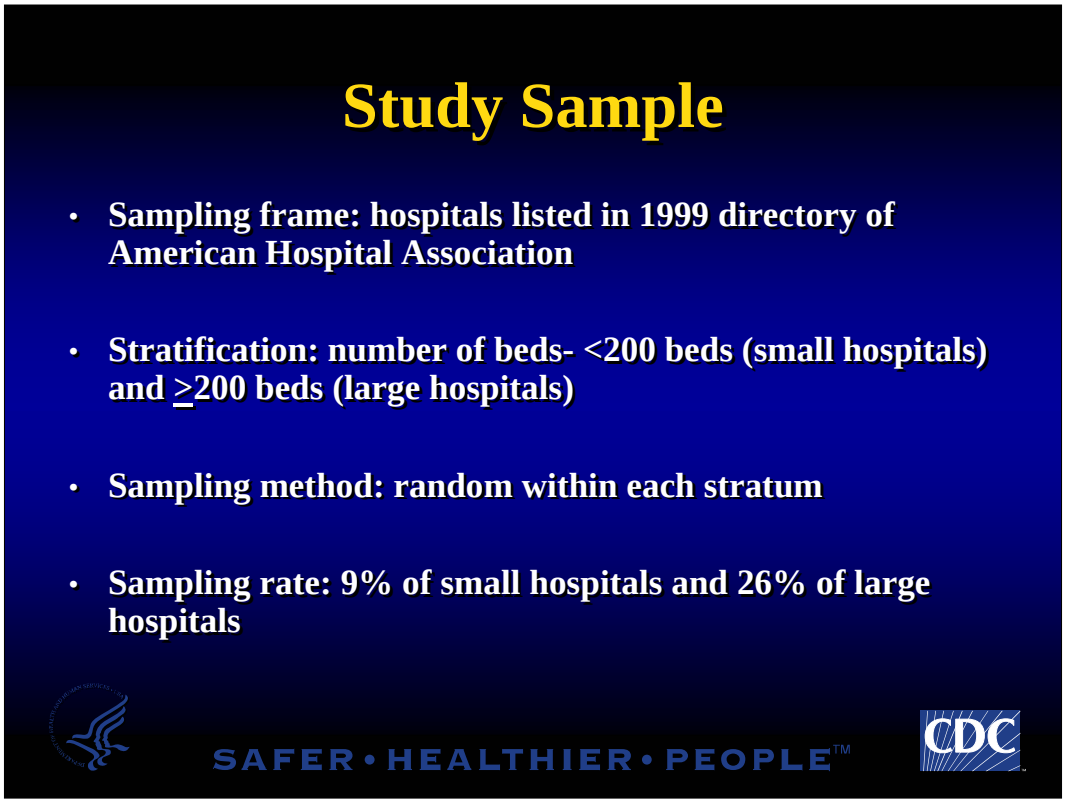
•… evaluate various post-test issues, and

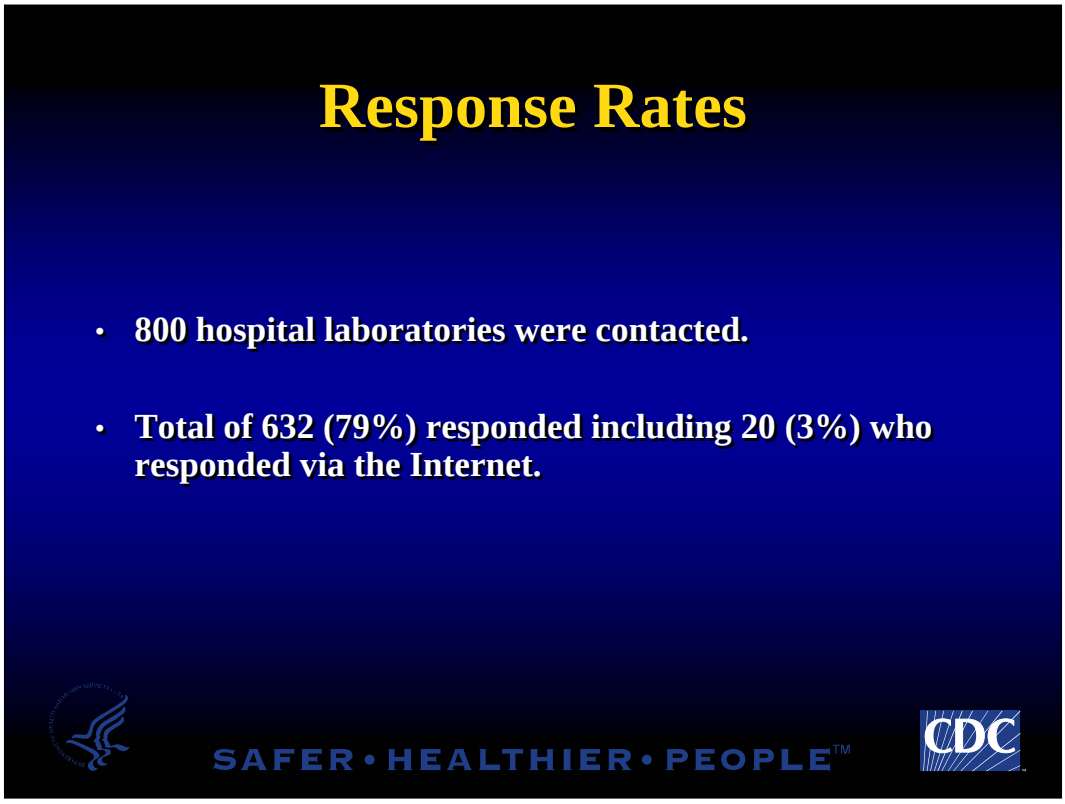
•and assess some testing practices critical to patients' management.



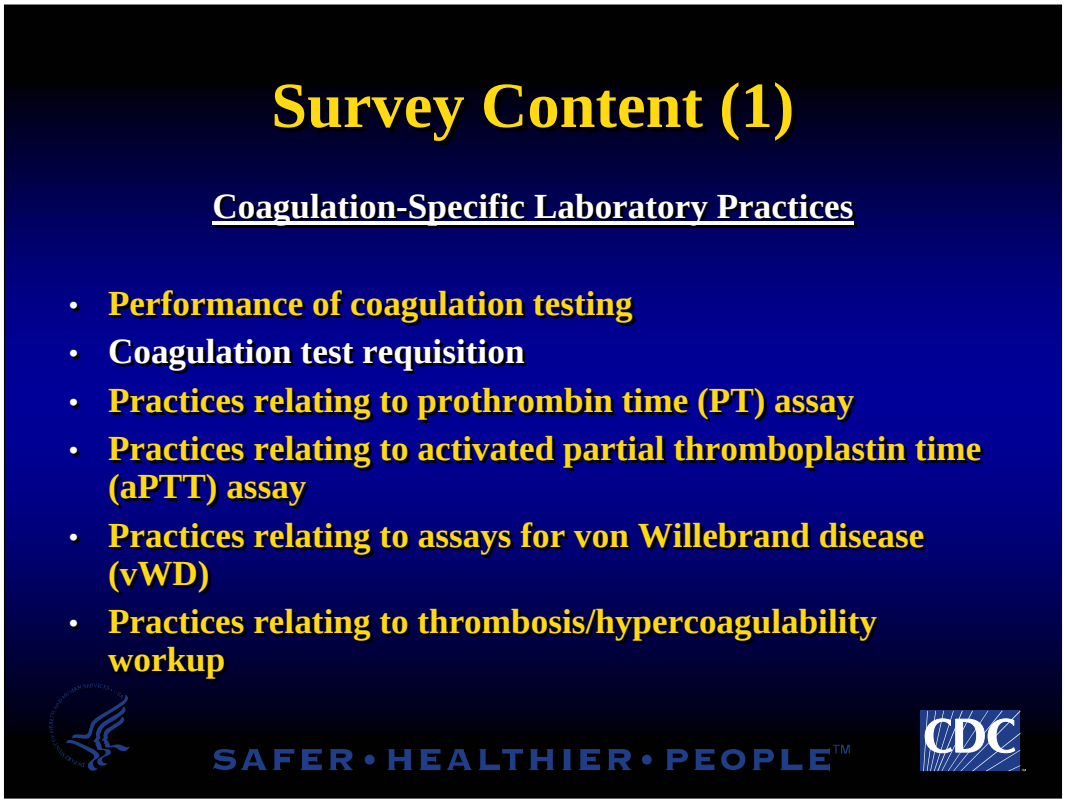
Hospitals listed in the 1999 directory of the American Hospital Association were used as the sampling frame.

We stratified hospitals into 2; those with less than 200 beds, labeled as “small” hospitals and those with equal to or more than 200 beds, labeled as “large” hospitals.

We randomly selected hospitals from these 2 strata—sampling 9% of small and 26% of large hospitals.

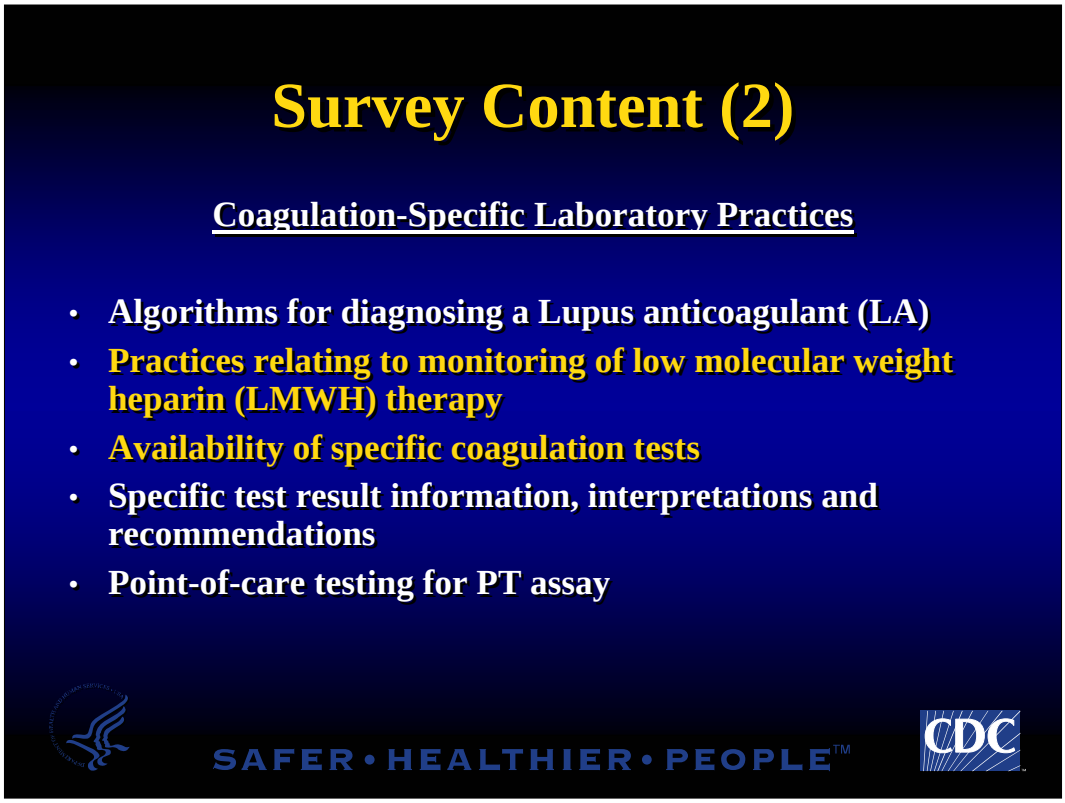


Of the 800 hospitals contacted, 632 responded including 20 via the Internet—giving rise to a total response rate of 79%.



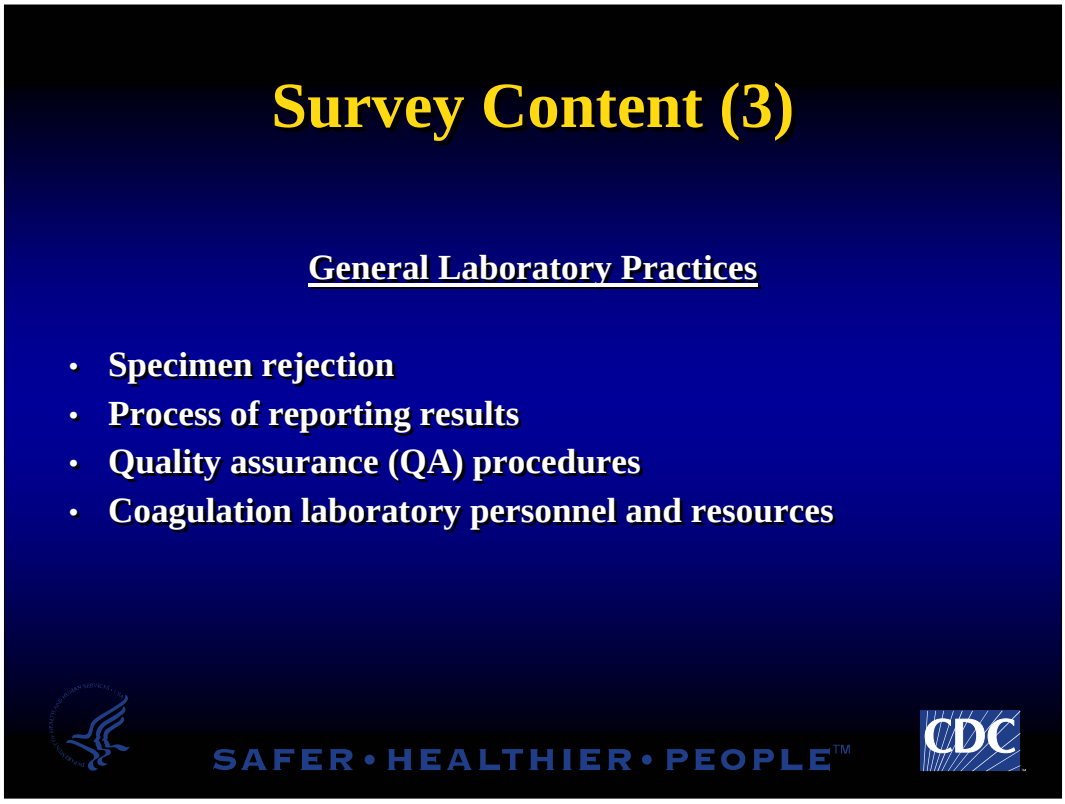
This slide shows some of the coagulation-specific laboratory issues this survey covered from the common PT and aPTT tests to less common testing practices to assess bleeding or thrombotic risk.

Highlighted in gold are the areas I will present during this talk.



This slide shows other coagulation-specific laboratory issues the survey addressed, ranging from practices to diagnose a Lupus anticoagulant and to monitor low molecular heparin therapy to point-of-care testing for PT assay.

Again, highlighted in gold are the areas I will cover during this presentation.



We also captured data on certain general laboratory practices, relating to specimen management, reporting of results, quality assurance and human and facility resources which, in the interest of time, I will not discuss at this time.

Performance of Coagulation Testing

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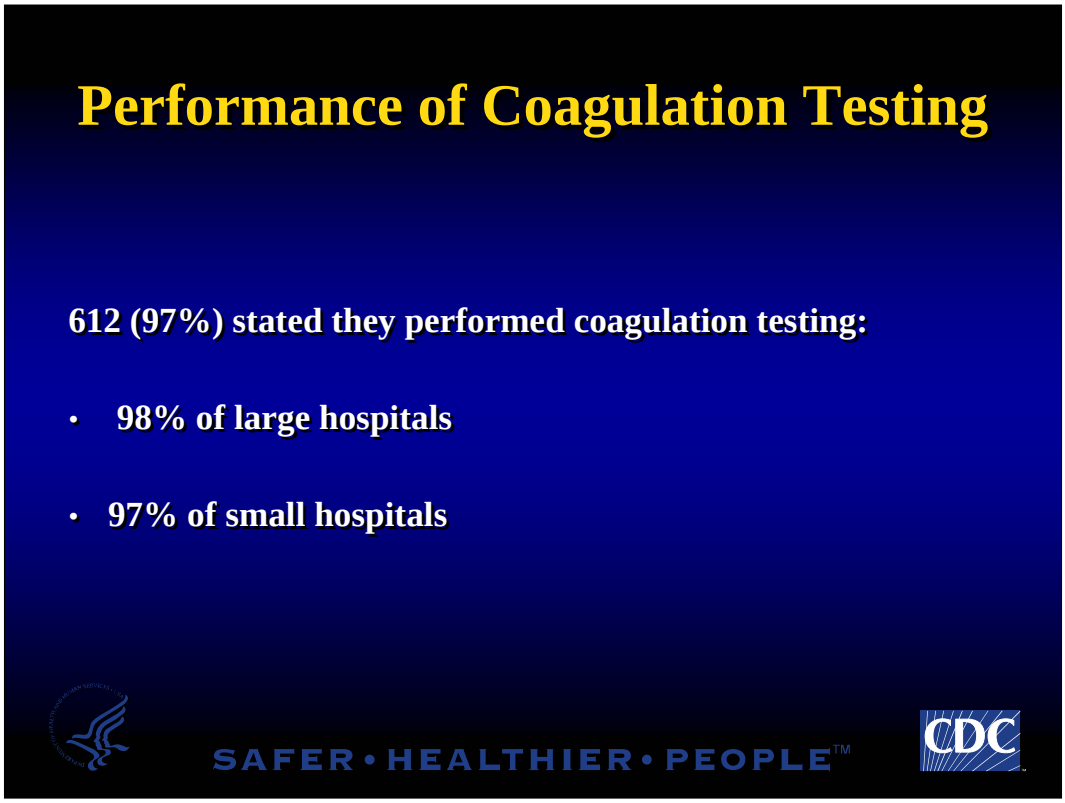

97% of the respondents stated performing coagulation testing. All subsequently analyzed data I will present relate to these respondents.

Practices Relating to PT Assay

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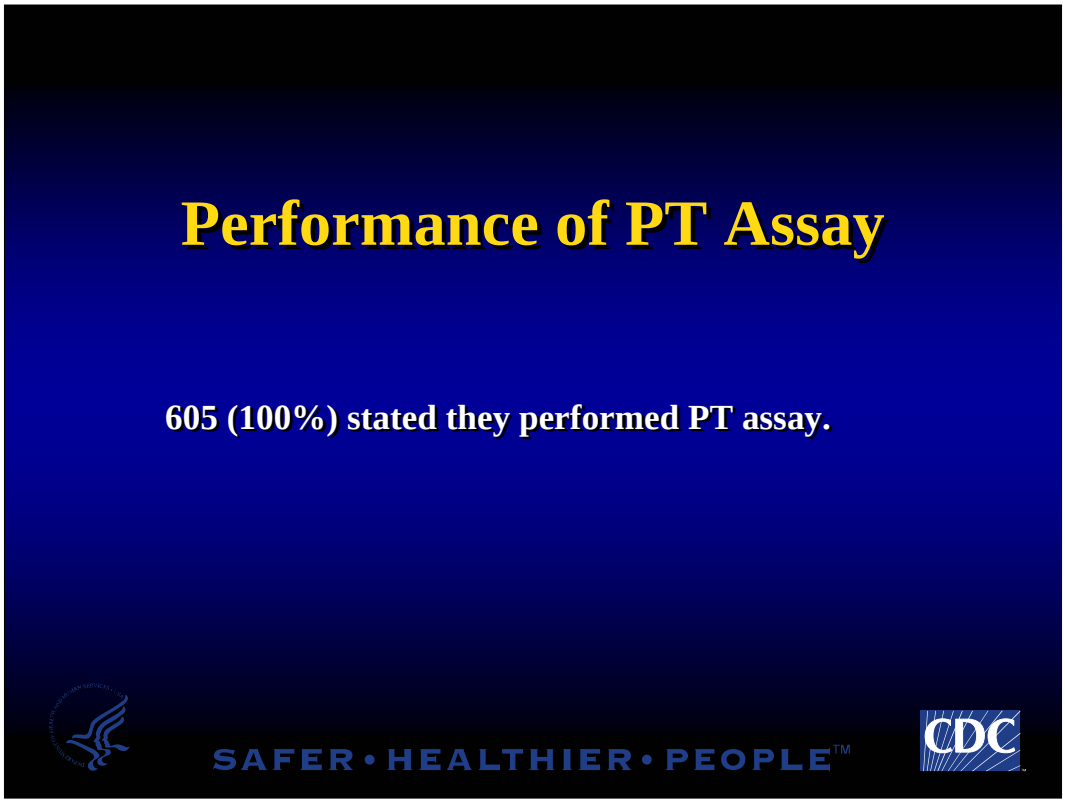
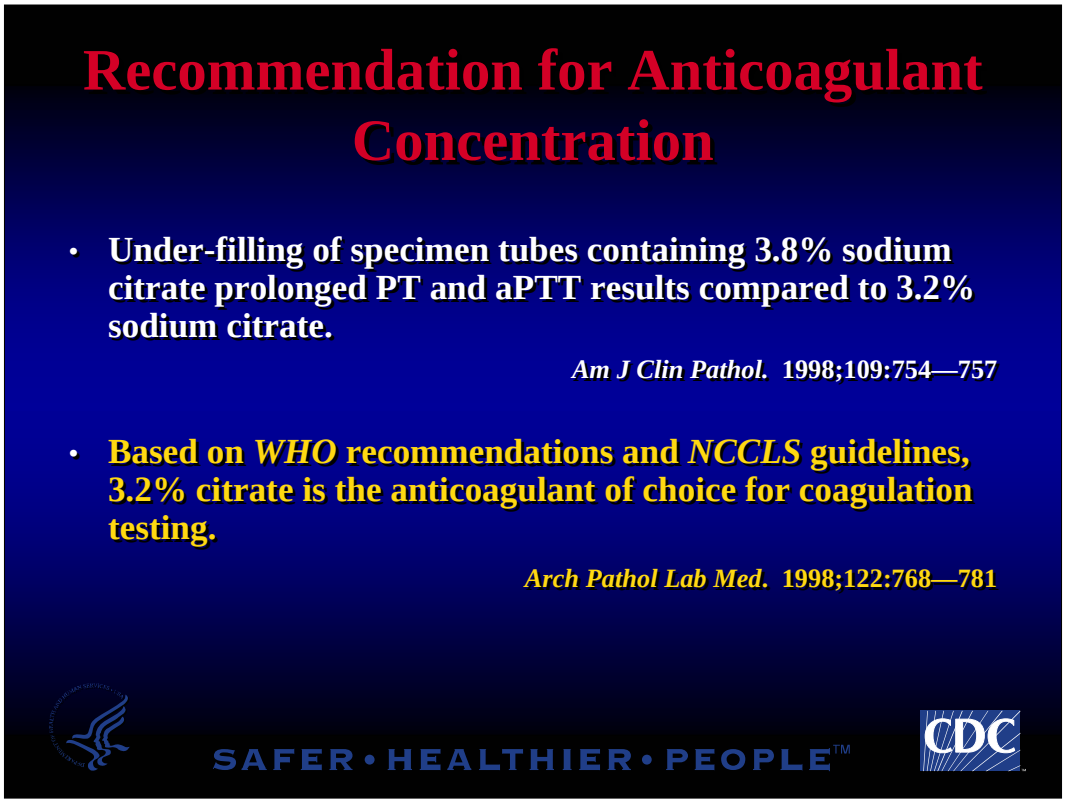
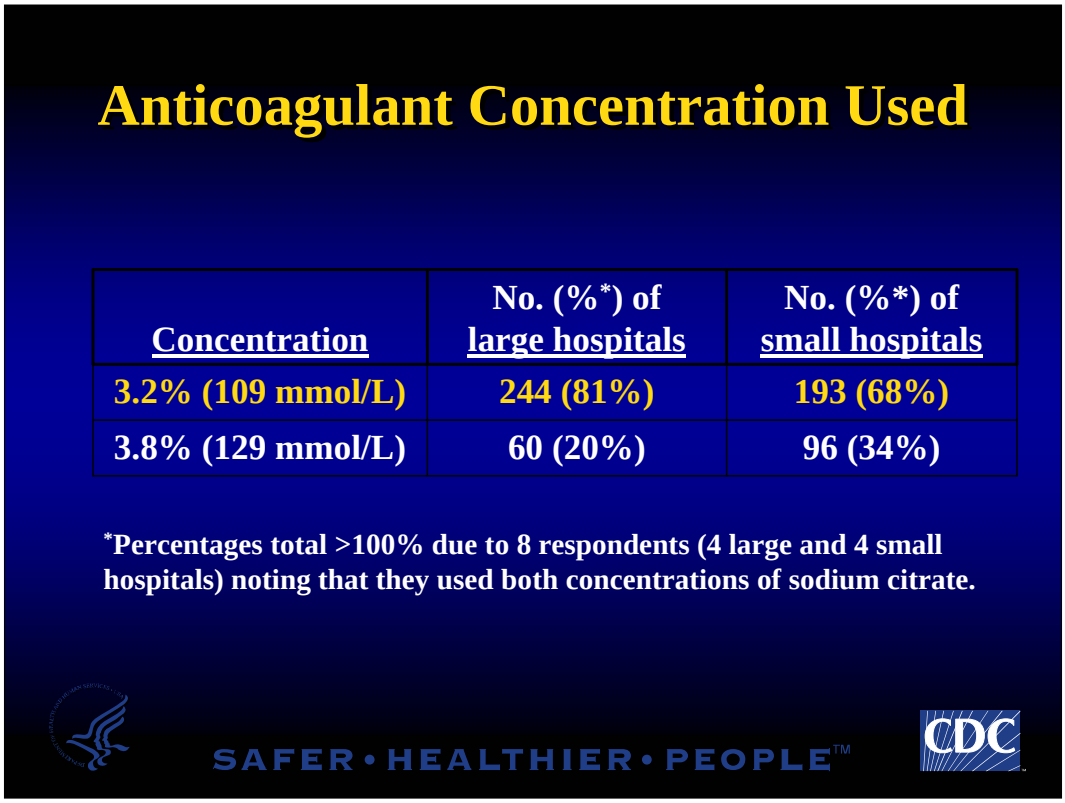


All reported performing PT assay.



Under-filling of 3.8% citrated tubes has been reported to prolong PT and especially aPTT results.

Both NCCLS and the World Health Organization recommend using 3.2% citrate as the anticoagulant of choice.



Although most respondents to this survey reported using 3.2% citrate, 20% of large hospitals and 34% of small hospitals reported using 3.8% citrate as the anticoagulant.

Exclusive Use of 3.2% Sodium Citrate

No. (%) of large hospitals	No. (%) of small hospitals	*P*
240 (80%)	189 (66%)	< 0.001

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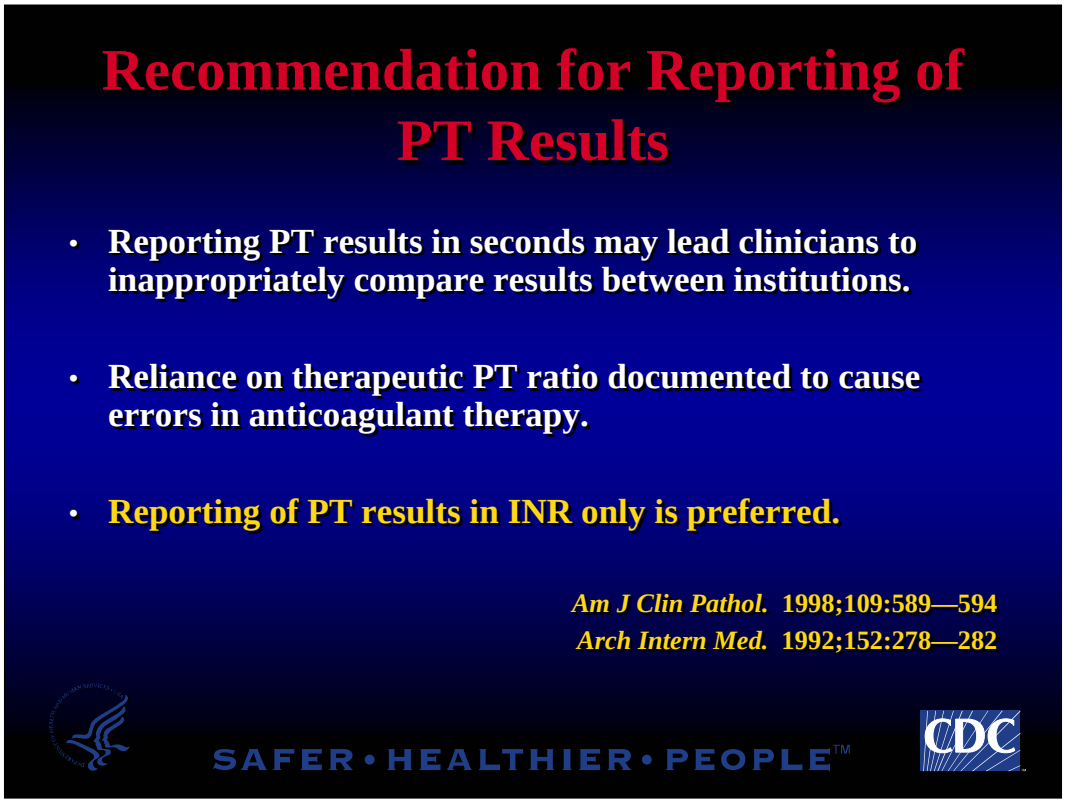
In agreement with NCCLS and WHO recommendations, a significantly greater proportion of large hospitals exclusively used 3.2% citrate compared to small hospitals.



Reporting of PT in seconds or as a therapeutic ratio is not recommended.

Current recommendation is that PT results be reported in international normalized ratio or INR only.

Reporting of PT Results (1)

Results reported in	No. (Proportion)
International normalized ratio (INR)	601 (100%)
Seconds	577 (97%)
Therapeutic PT ratio	77 (16%)

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Although , in agreement with the accepted practice, all respondents noted that they reported PT results in INR, contrary to current recommendations, 97% also reported PT results in seconds and 16% reported results as therapeutic PT ratio.

Reporting of PT Results (2)

Format Used to Report PT Result by US Hospitals and Canadian Medical Laboratories*

Reporting format	US, 2001 (n = 626)	Canada, 1996 (n = 649)	Canada, 1992 (n = 857)
Seconds and INR	80%	60%	36%
Seconds, INR and PT ratio	12%	–	–
Not specified	4%	–	–
INR only	3%	36%	15%
INR and PT ratio	0.5%	1.5%	6%
Seconds only	0%	<1%	36%
PT ratio only	0%	1%	7%

**Am J Clin Pathol.* 1998;109:589—594*
**Am J Hematol.* 1995;48:237—239*

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This slide shows how respondents stated reporting PT results in this survey in comparison with 2 surveys of Canadian medical laboratories.

3% of the respondents in our survey noted using only INR to report PT results. Compare this result with the a rate of 15% in a 1992 Canadian survey and a rate of 36% in a 1996 Canadian survey.

Reference Interval for PT Assay (1)

- 568 (92%) conducted in-house evaluations to establish reference intervals for PT assay.

No. (%) of large hospitals	No. (%) of small hospitals	*P*
291 (97%)	277 (87%)	<0.001

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92% reported conducting in-house evaluations to establish reference intervals for PT assay, which is the accepted laboratory practice for first use of all assays. A significantly greater proportion of the large hospitals did so compared to the small hospital respondents.

Reference Interval for PT Assay (2)

Other method to establish reference interval	No. (%)
Manufacturer's instructions	31 (57%)
Published values	16 (30%)
Others	10 (19%)

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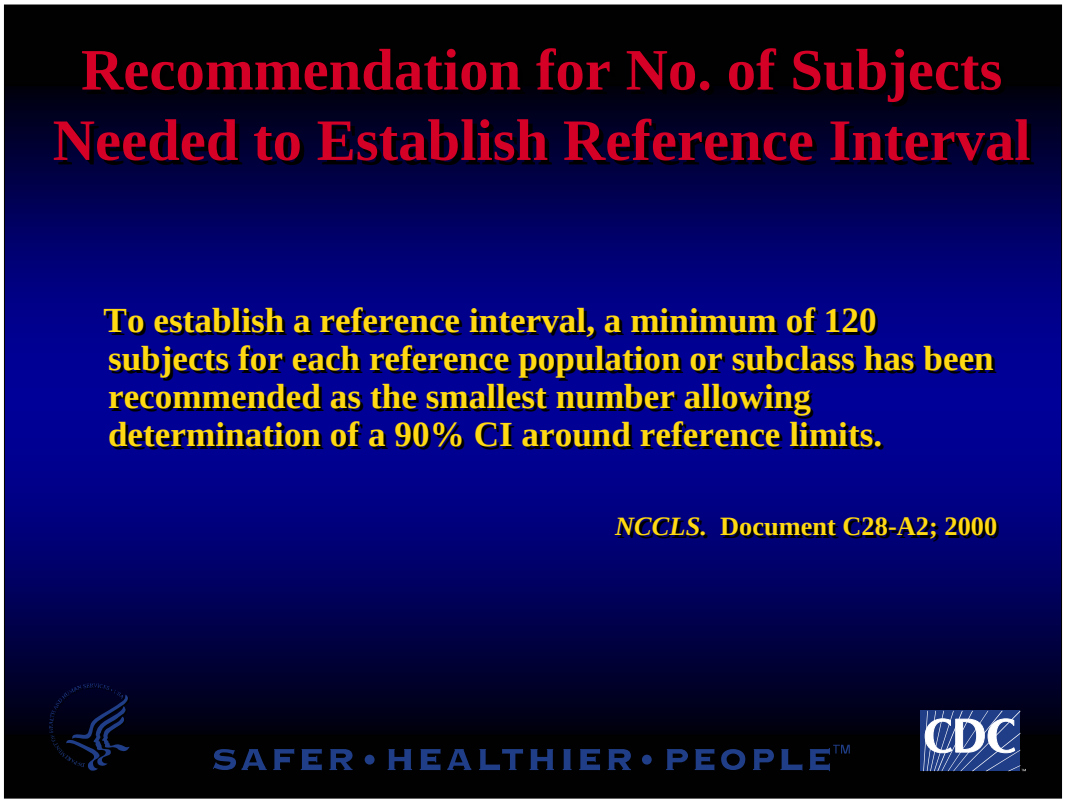
Of those noting other methods to establish the reference interval for their PT assay, ~60% used manufacturer's instruction and 30% used published values to arrive at their reference range.



To establish the reference interval for any quantitative assay, NCCLS recommends using a minimum of 120 subjects to allow determination of a 90% confidence interval around reference limits.

Reference Interval for PT Assay (3)

Min number of subjects used	No. (%) of large hospitals	No. (%) of small hospitals
20 or fewer	24 (8%)	62 (25%)
21-39	112 (38%)	123 (49%)
40-59	88 (30%)	40 (16%)
60-119	56 (19%)	18 (7%)
120-199	11 (4%)	4 (2%)
200 or more	5 (2%)	4 (2%)

Response patterns of large and small hospitals were different ($P < 0.001$).

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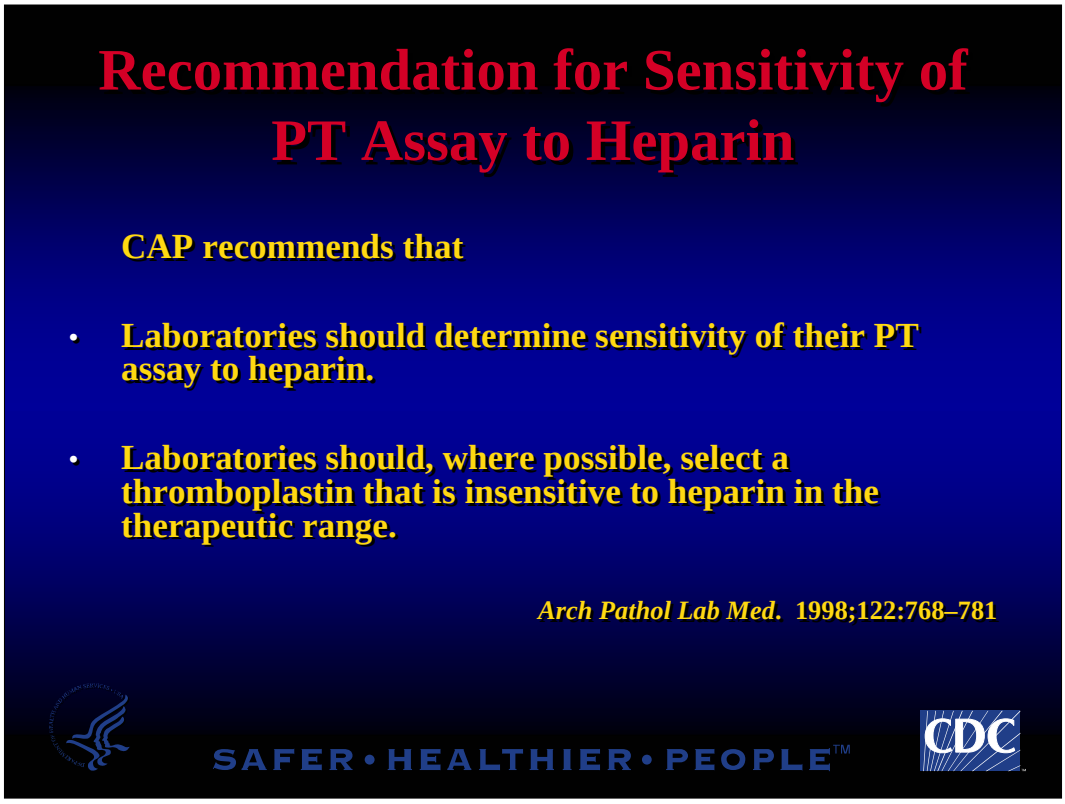
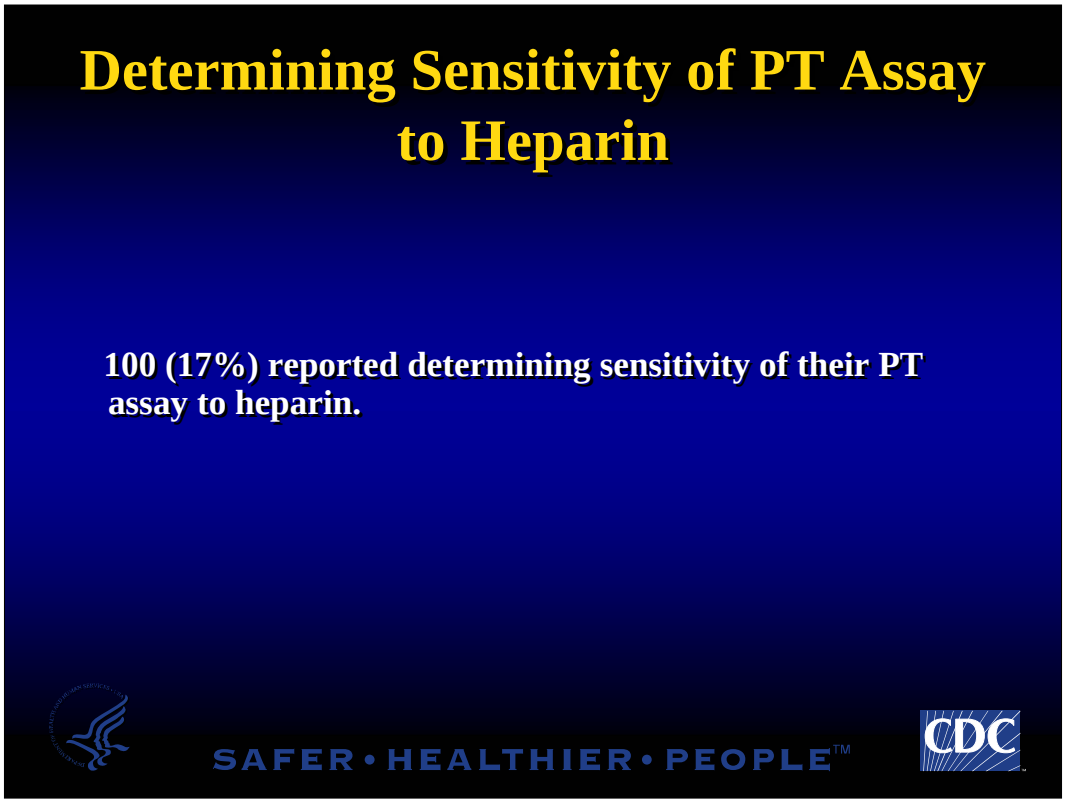
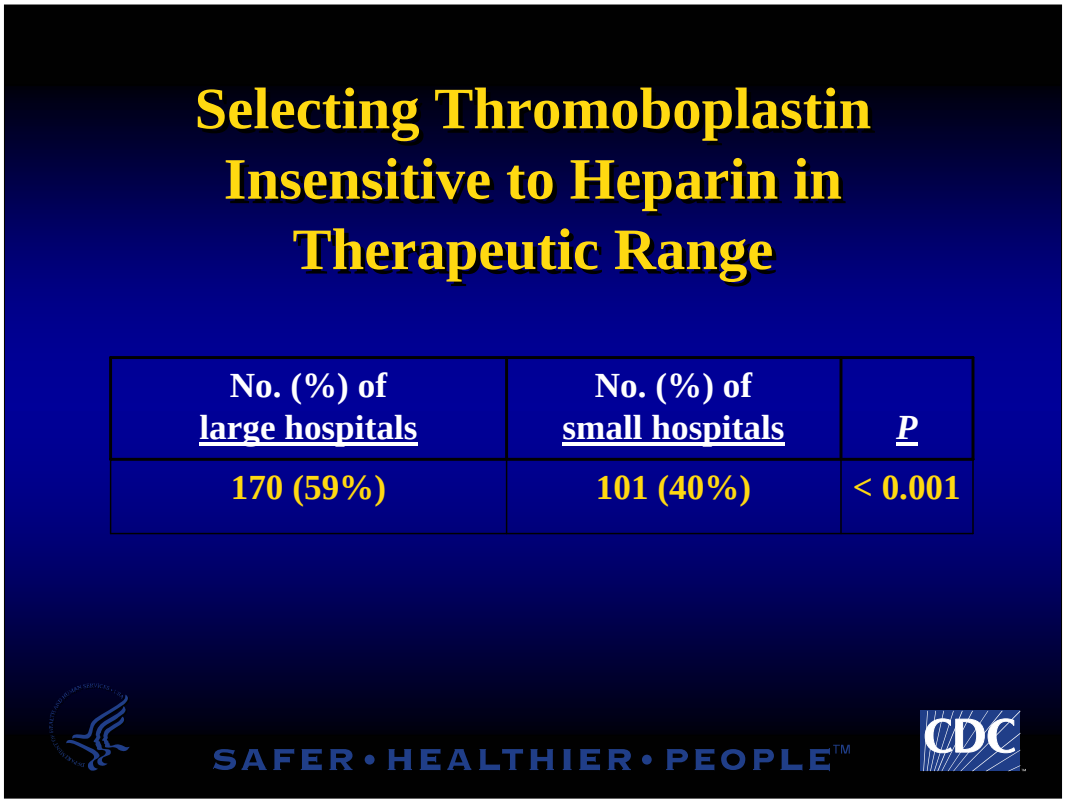
5% of respondents used at least 120 subject to establish the reference interval for their PT assay. The large hospital respondents tended to use greater number of subject to establish their reference intervals compared to the small hospitals. In fact, response patterns of the large and small hospital respondents were significantly different.



College of American Pathologists, CAP, recommends determining sensitivity of the PT assay to heparin, and they also recommend that, where possible, laboratories select a thromboplastin that is insensitive to heparin in the therapeutic range. In agreement with the 1st recommendation, …

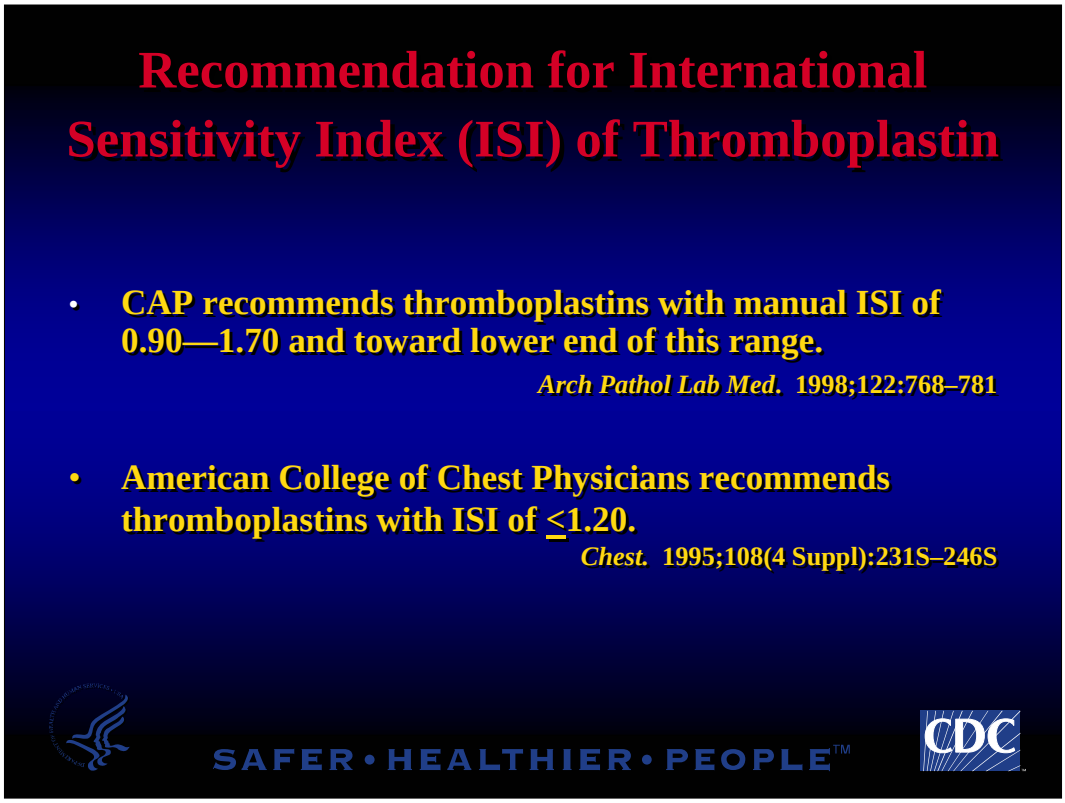


… 17% of the respondents reported determining sensitivity of their PT assay to heparin. Consistent with CAP recommendation, …



… ~50% of all respondents selected thromboplastins that were insensitive to heparin in the therapeutic range.

Responses from the large and small hospital respondents were significantly different. While ~60% of large hospitals reported selecting insensitive thromboplastins, 40% of small hospitals reported doing so.



Due to increased variability in INR resulting from ISI values deviating significantly from 1, various groups have recommended using thromboplastins with ISIs closer to 1.

CAP recommends thromboplastins with ISI not exceeding 1.70, while American College of Chest Physicians recommends an ISI not in excess of 1.20.

ISI of ≤1.70

247 (44%) reported ISI of ≤1.70 .

No. (%) of large hospitals	No. (%) of small hospitals	*P*
151 (50%)	96 (36%)	0.001

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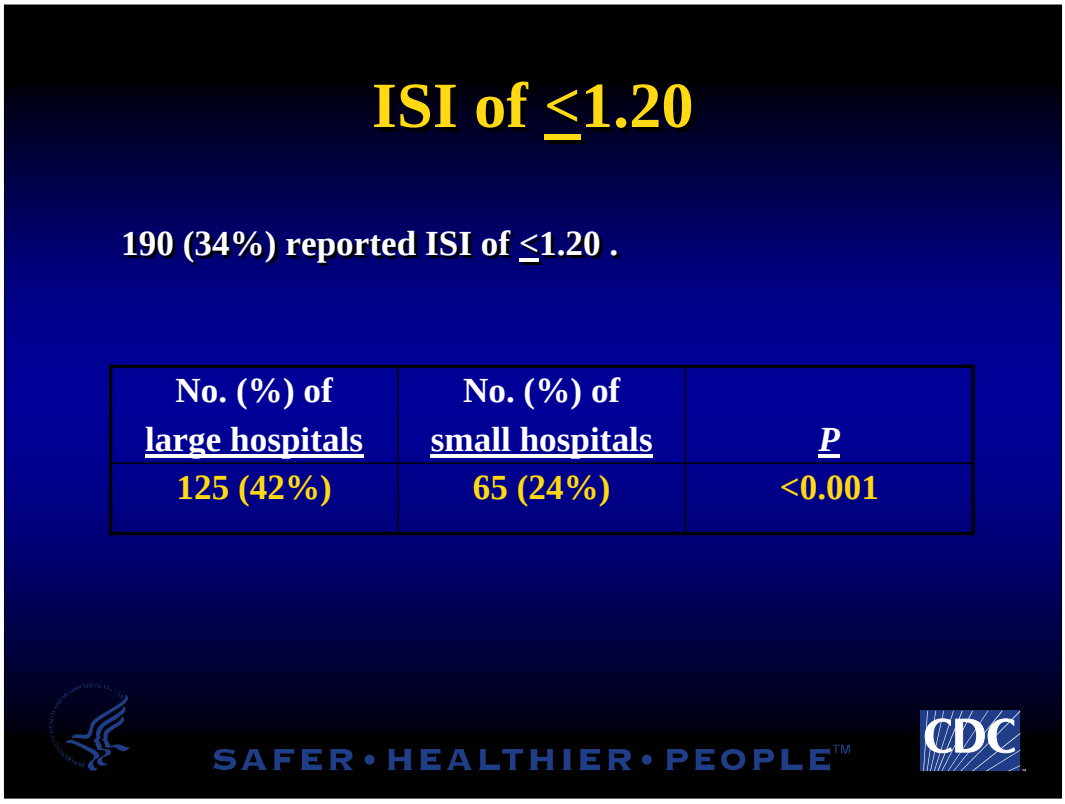
Consistent with CAP recommendation, 44% reported ISIs of less than 1.71 for their current thromboplastin lots. A significantly greater proportion of the large hospitals reported doing so compared to the small hospitals.



In agreement with recommendation of the American College of Chest Physicians, 34% reported ISIs of less than 1.21 for their current thromboplastin lots. Again, a significantly greater proportion of the large hospitals reported doing so compared to the small hospitals.

Practices Relating to aPTT Assay

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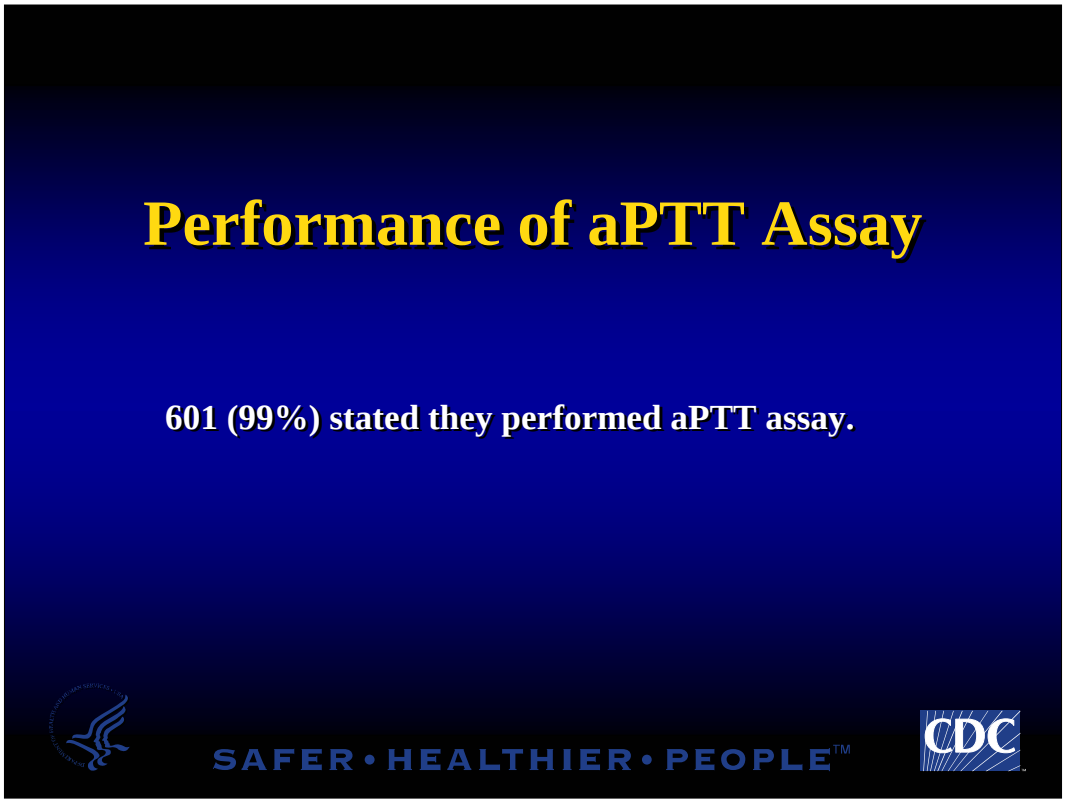

99% reported performing aPTT assay.

Based on current recommendations, each laboratory should establish an individual therapeutic range for heparin specific to its own reagent and instrument system. In agreement with these recommendations, …

Therapeutic Range for Heparin

355 (64%) reported they had an aPTT therapeutic range for heparin when monitoring heparin therapy.

No. (%) of large hospitals	No. (%) of small hospitals	*P*
213 (73%)	142 (53%)	<0.001

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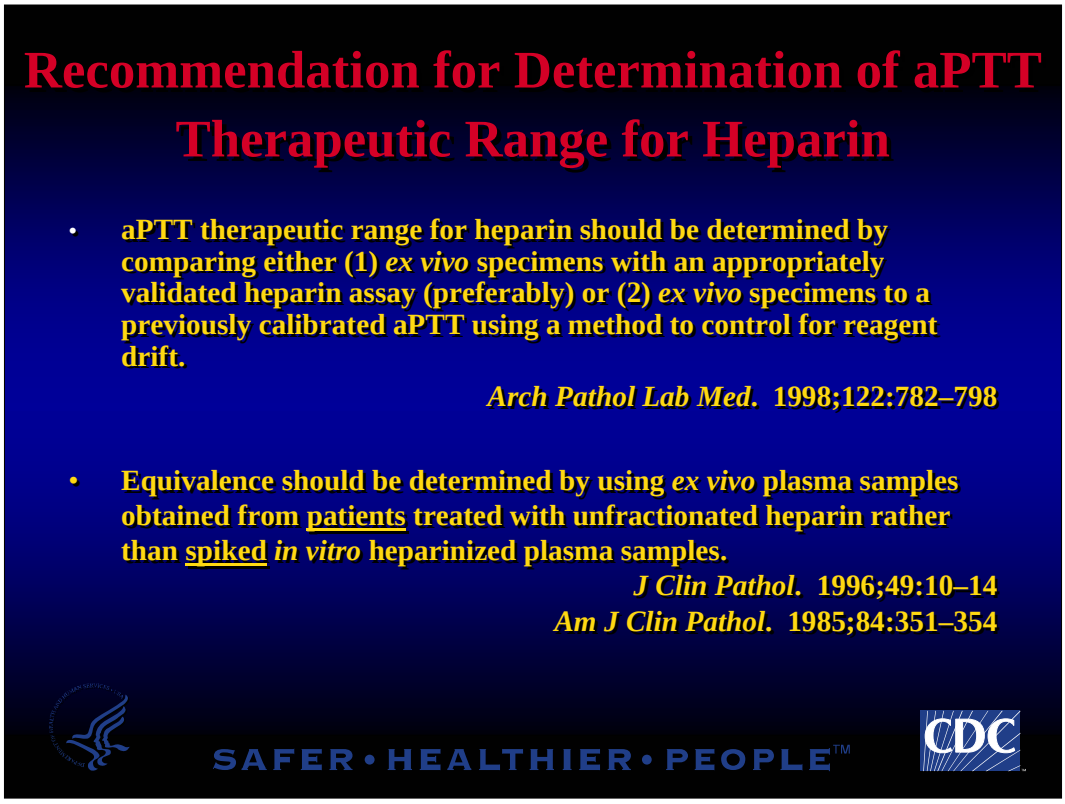
… 64% reported they had an aPTT therapeutic range for heparin when monitoring heparin therapy. A significantly greater proportion of the large hospitals reported doing so compared to the small hospital. Half of the small hospital respondents reported not having an aPTT therapeutic range for heparin.



Based on current recommendations, *ex vivo* plasma samples of patients on heparin therapy should be used to determine the aPTT therapeutic range for heparin. Heparin-spiked *in vitro* plasma samples should not be used for this purpose. In agreement with these recommendations …

How aPTT Therapeutic Range for Heparin was Determined

Practices to determine aPTT therapeutic range for heparin	Large hospitals	Small hospitals	*P*
Using samples from patients on heparin therapy to compare a new reagent lot to an old reagent lot	116 (66%)	57 (50%)	0.007
Using heparin spiked samples to compare a new reagent lot to an old reagent lot	80 (47%)	50 (46%)	0.881
Performing anti-Xa assay	76 (47%)	17 (18%)	<0.001
Using heparin spiked samples to compare a new heparin lot to an old heparin lot	19 (12%)	22 (21%)	0.038
Using samples from patients on heparin therapy to compare a new heparin lot to an old heparin lot	19 (11%)	14 (14%)	0.602
Performing protamine sulfate titration	17 (11%)	5 (5%)	0.134

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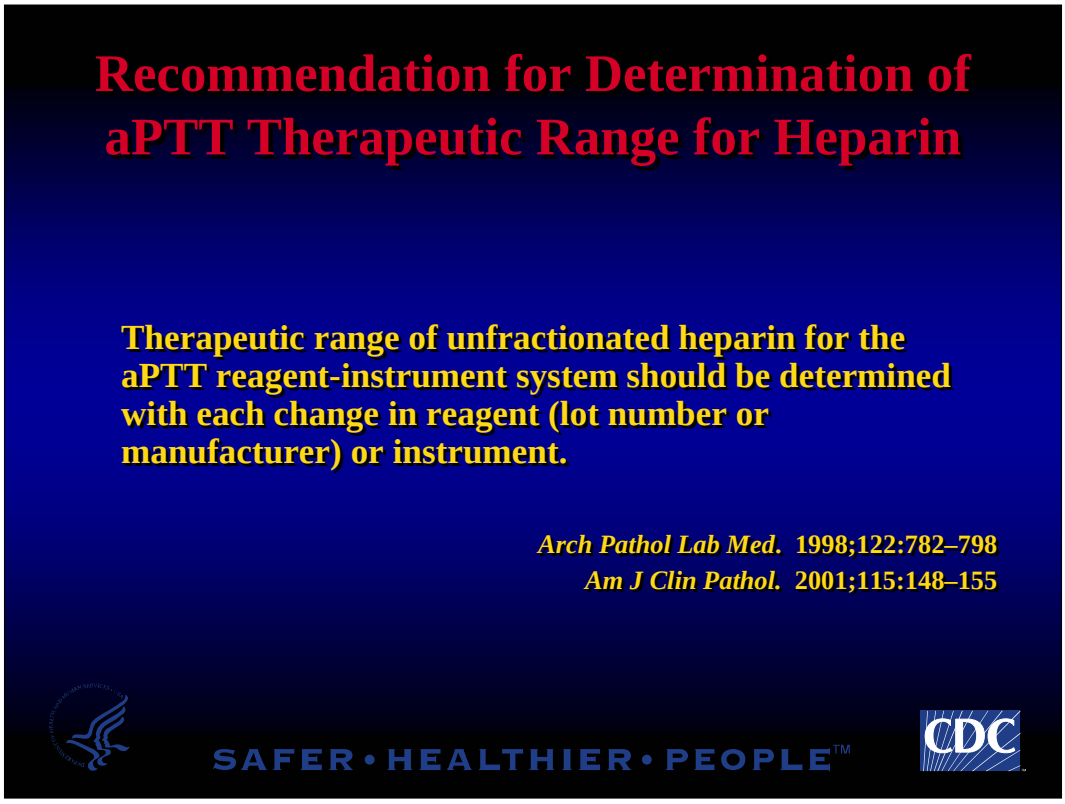
… 66% of the large hospitals reported using *ex vivo* plasma samples from patients on heparin therapy compared to 50% of the small hospitals for comparing a new to an old reagent lot. However, ~50% of the respondents reported using *in vitro* heparin-spiked samples to do the same —against current recommendations.

In agreement with current recommendations, 11—14% of the respondents reported using *ex vivo* plasma samples from patients on heparin therapy to compare a new to an old heparin lot. However, 12% of the large hospitals and 21% of the small hospitals used *in vitro* heparin-spiked samples to do the same—against current recommendations.

~50% of the large hospitals and ~20% of the small hospitals reported performing anti-Xa assay.



Based on current recommendations, therapeutic range of unfractionated heparin for the aPTT reagent-instrument system should be determined with each change in reagent lot number, reagent manufacturer or testing instrument. In agreement with these recommendations, …

When aPTT Therapeutic Range for Heparin was Reconfirmed

When reconfirm the aPTT therapeutic range for heparin	No. (%) of hospitals
When new instrumentation is used	282 (79%)
When new reagent lots are used	269 (75%)
When new reagents are used	181 (51%)
After a specified time period	77 (22%)
None of the above	29 (8%)

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… ~3/4 of the respondents reported reconfirming aPTT therapeutic range for heparin when new test instrument or new reagent lots were used, and ~50% did so when new reagents were used.

NCCLS recommends that samples be assayed for aPTT within 4 hours after phlebotomy if centrifuged within 1 hour of collection. In agreement with this recommendation …

Specimen Management for aPTT Assay

Practices used for aPTT assay specimen management	Large hospitals	Small hospitals	*P*
Specimens assayed within 4 h after phlebotomy	276 (96%)	259 (97%)	0.490
Specimens centrifuged within 1 h of collection	229 (84%)	238 (92%)	0.007
Specimens kept at room temperature prior to testing	223 (84%)	196 (80%)	0.188
Specimens kept at 4 °C prior to testing	47 (20%)	54 (24%)	0.335

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… 96—97% reported assaying specimens for aPTT within 4 hours after phlebotomy, and ~90% reported centrifuging specimens within 1 hour of collection. A significantly greater proportion of the small hospitals reported centrifuging specimens within 1 hour of collection compared to the large hospitals.

80—84% reported keeping specimens at room temperature before aPTT assay while 20—24% reported keeping specimens at 4 °C.

Practices Relating to Assays for von Willebrand Disease (vWD)

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Performance/Provision of von Willebrand Factor (vWF) Assays

Assay	No. (%) of large hospitals	No. (%) of large hospitals	*P*
Performance of vWF antigen	35 (12%)	1 (0.4%)	<0.001
Performance of vWF (Ristocetin cofactor) activity	41 (14%)	1 (0.4%)	<0.001
Provision of results for vWF multimers	10 (3%)	1 (0.4%)	0.007

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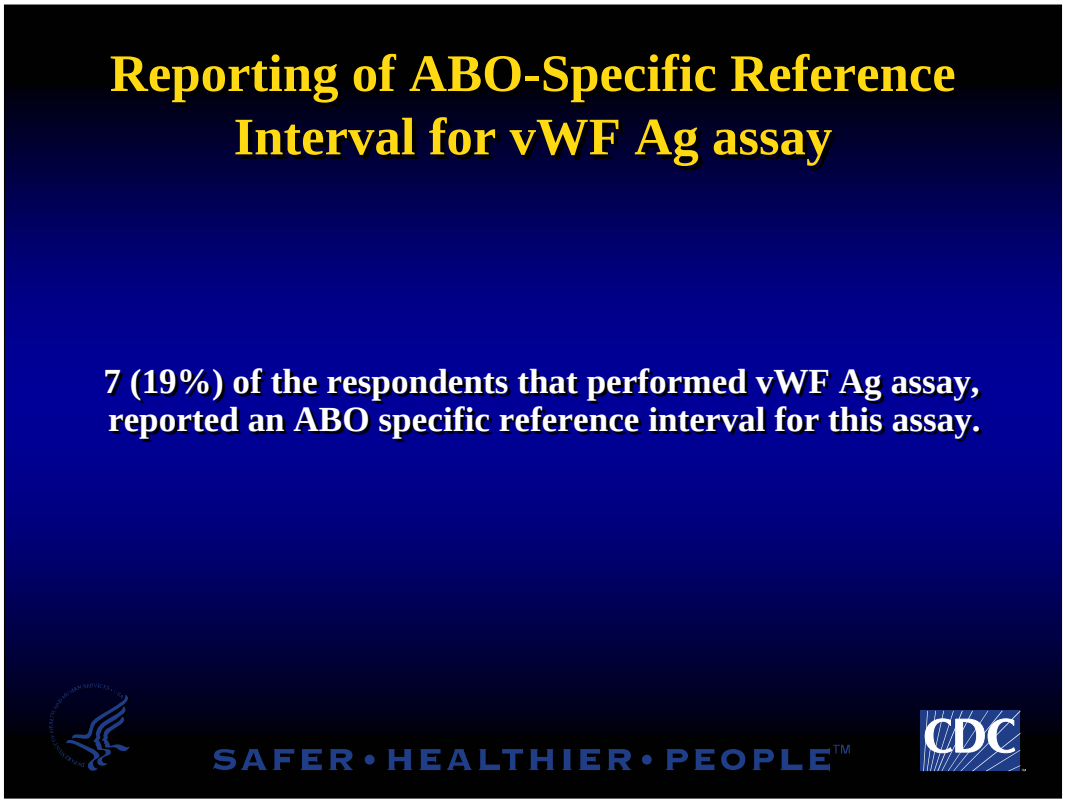
6% of the respondents reported performing von Willebrand factor antigen assay, and 7% reported performing assay for von Willebrand factor or Ristocetin cofactor activity.

2% of the respondents reported providing von Willebrand factor multimers results.

With all 3 assays, a significantly greater proportion of the large hospital respondents reported performing or providing results for them compared to the small hospital respondents.



~20% the respondents performing von Willebrand factor antigen assay reported an ABO specific reference interval for this assay—considering that blood type appears to affect concentration of von Willebrand factor antigen.

When vWF Multimers were Assayed

When vWF Multimers were Assayed	No. (%)
Only when ordered by a clinician	9 (82%)
When Ristocetin cofactor is decreased	3 (38%)
When Ristocetin cofactor is disproportionately decreased relative to vWF Ag	2 (29%)
When antigen and activity are both low	2 (25%)
Only if Ristocetin induced platelet aggregation indicates a Type II B vWD	1 (13%)

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~80% of the respondents noted that they provided von Willebrand factor multimers results only when ordered by a clinician, and ~40% did so when Ristocetin cofactor was decreased.

~30% provided multimers results when Ristocetin cofactor was disproportionately decreased relative to von Willebrand factor antigen, and ¼ did so when von Willebrand factor antigen and activity were both low.

Practices Relating to Thrombosis and Hypercoagulability Workup

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Performance of Functional Test for Protein S Before Antigenic Assay

32 (5%) performed functional test for Protein S before antigenic assay:

No. (%) of large hospitals	No. (%) of small hospitals	*P*
31 (10%)	1 (0.3%)	<0.001

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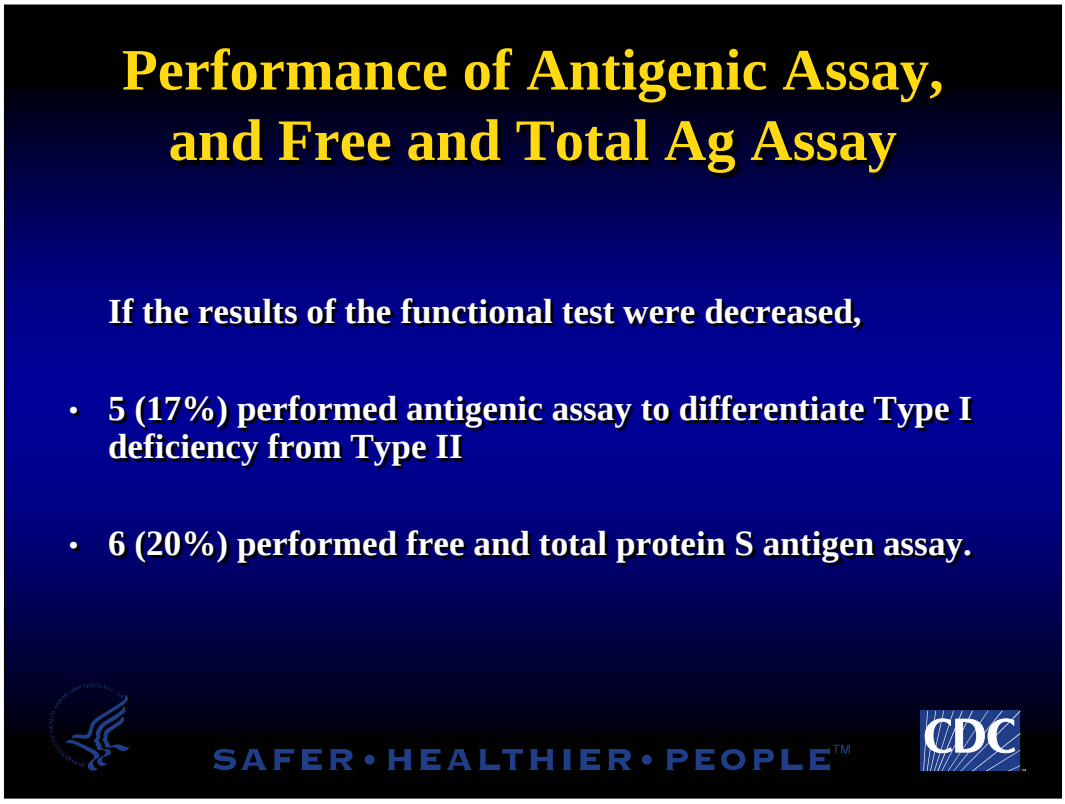
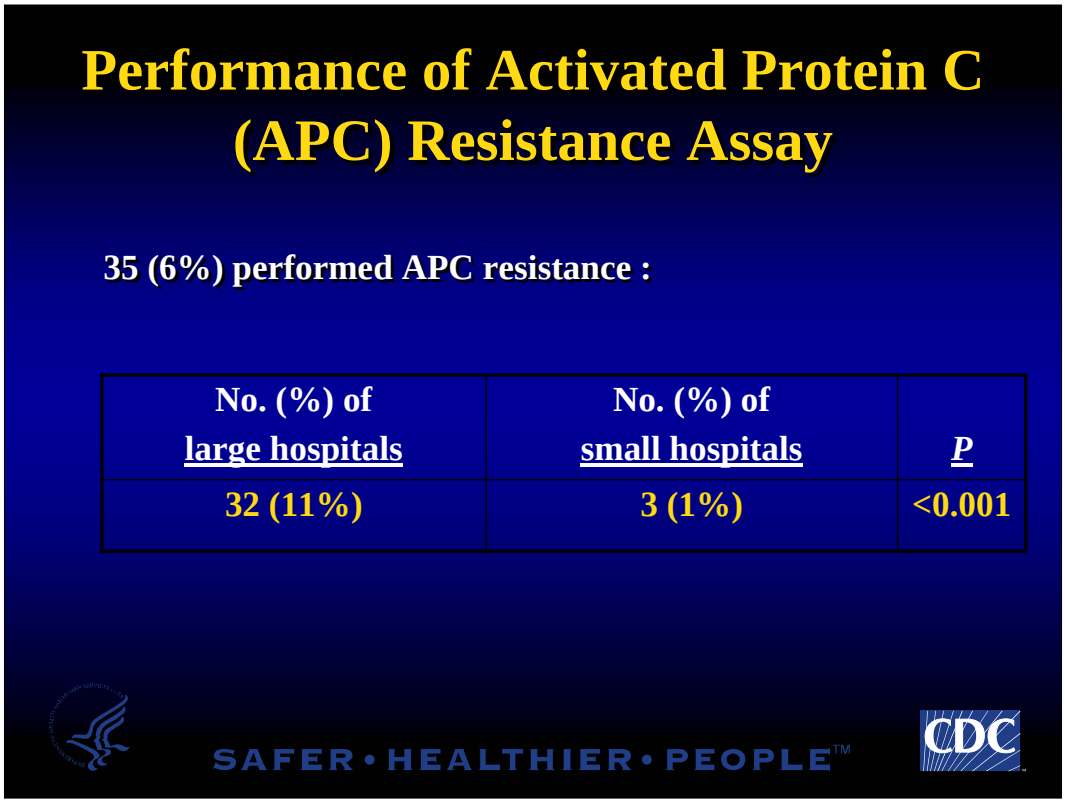
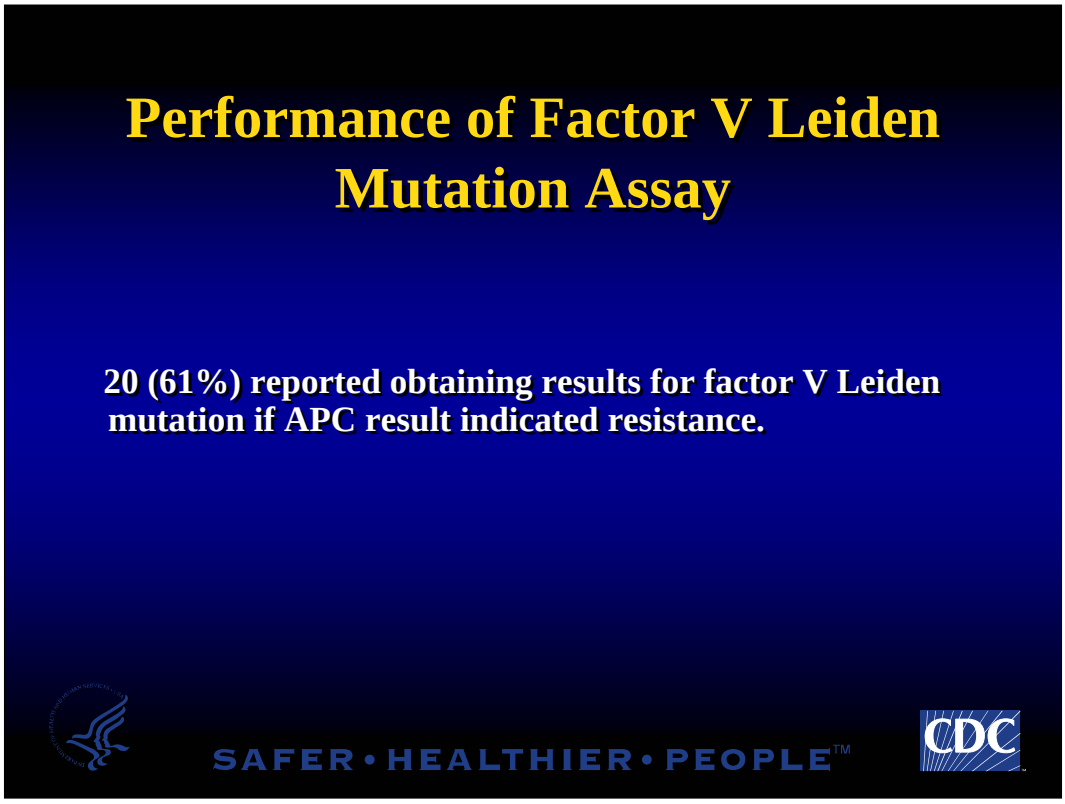
5% reported performing a functional test for protein S before antigenic assay. A significantly greater proportion of the large hospitals did so compared with the small hospitals.



If the results of the functional test were decreased, 17% performed antigenic assay to differentiate Type I deficiency from Type II and 20% performed free and total protein S antigen assay.



6% reported performing activated protein C or APC resistance assay. A significantly greater proportion of the large hospital respondents did so compared with their small hospital counterpart.



~60% reported obtaining results for factor V Leiden mutation if the APC result indicated resistance. This was an interesting finding since the clinical utility of performing factor V Leiden mutation after observation of APC resistance has not been established.

Practices Relating to Monitoring of Low Molecular Weight Heparin (LMWH) Therapy

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Monitoring of LMWH Therapy

82 (14%) reported monitoring LMWH therapy:

No. (%) of large hospitals	No. (%) of small hospitals	*P*
55 (19%)	27 (10%)	0.002

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14% reported monitoring low molecular weight heparin therapy. A significantly greater proportion of the large hospitals did so compared with the small hospitals.

To monitor low molecular weight heparin, CAP recommends using a chromogenic anti–factor Xa assay, and they recommend against using an aPTT assay for the same purpose.

Assays Used to Monitor LMWH Therapy

Assay to monitor LMWH therapy	No. (%) of large hospitals	No. (%) of small hospitals	*P*
aPTT	23 (58%)	24 (96%)	0.001
Anti-Xa	32 (65%)	3 (18%)	0.001
Factor Xa (inhibitor assay)	3 (8%)	1 (6%)	0.795
Thrombin inhibitor assay (HEP test)	0	0	–

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A significantly greater proportion of the large hospitals performed *anti-Xa assay*, in agreement with CAP recommendation, to monitor low molecular weight heparin compared with the small hospitals.

A significantly greater proportion of the small hospitals performed *aPTT assay*, in disagreement with CAP recommendation, to monitor low molecular weight heparin compared with the large hospitals.

The apparent reason small hospitals mostly used aPTT assay in lieu of anti-Xa assay to monitor low molecular weight heparin therapy may be that few of them even perform an in-house anti-Xa assay—as reported in this survey.

Calibrator Used for Anti-Xa Assay

Calibrator	No. (Proportion)
LMWH supplied by pharmacy	19 (53%)
Internal standard LMWH	8 (22%)
Unfractionated heparin	5 (14%)
Internal standard unfractionated heparin	4 (11%)
Heparinoid	1 (3%)
Others	8 (22%)

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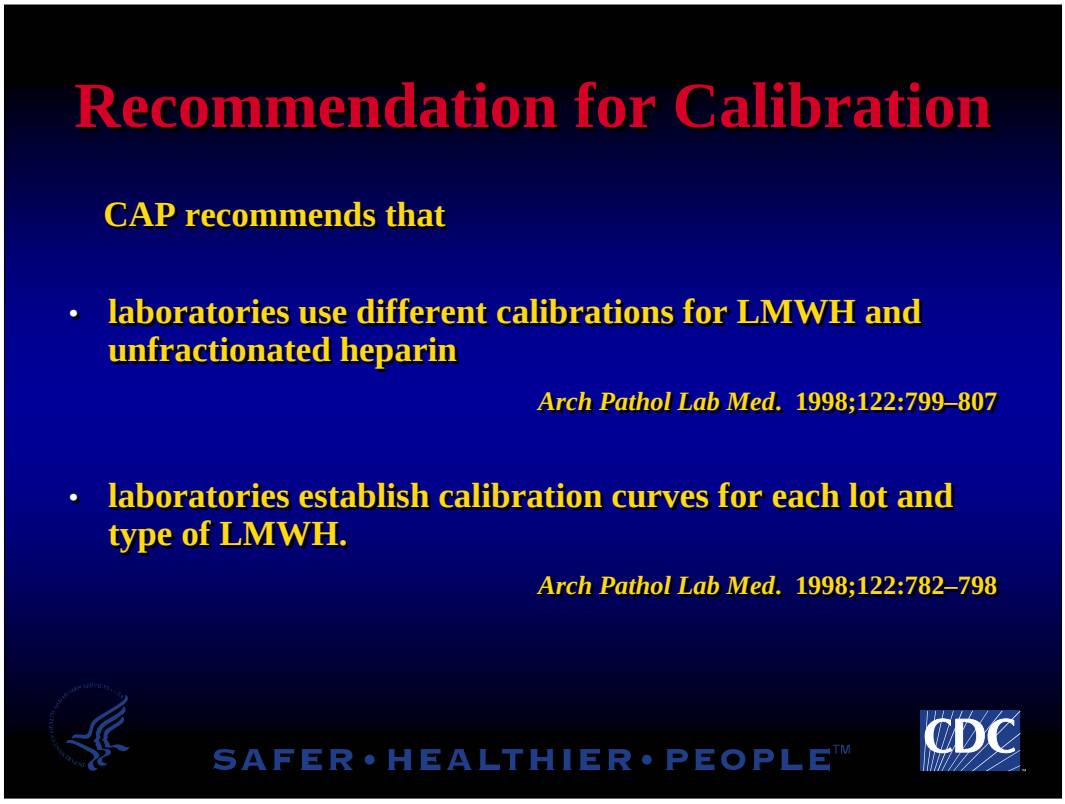
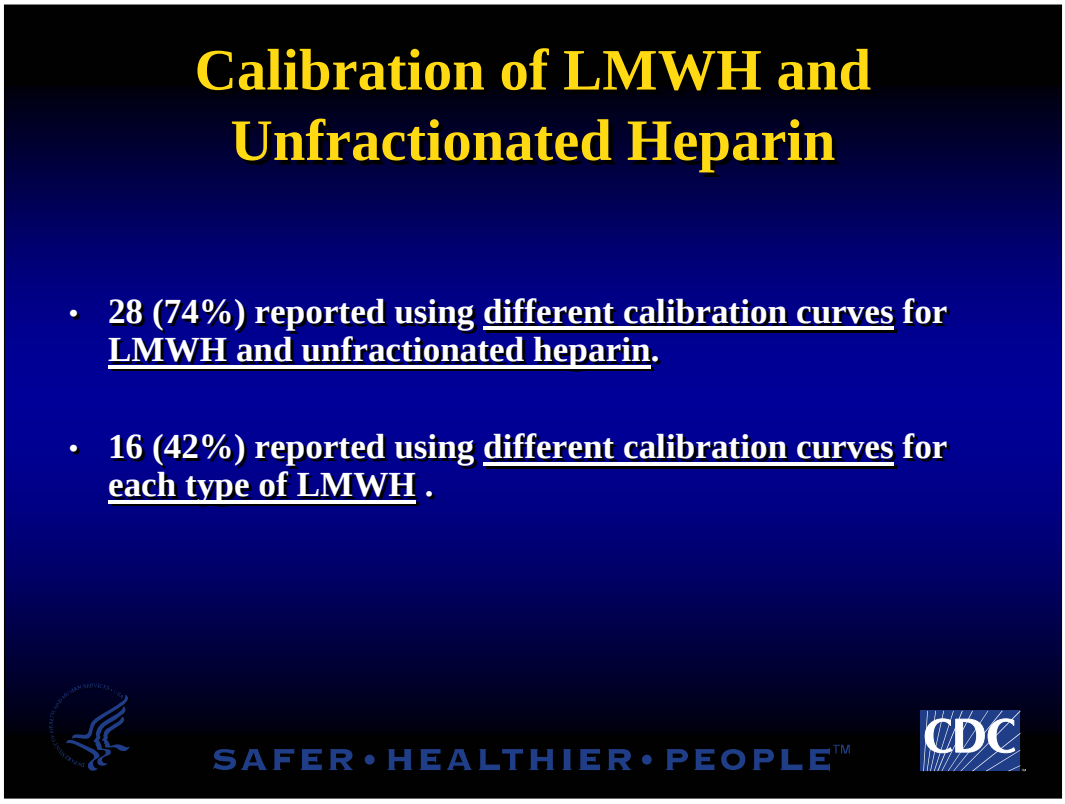
The majority, a little over 50%, used a low molecular weight heparin calibrator supplied by the pharmacy, and ~20% used another low molecular weight heparin standard.

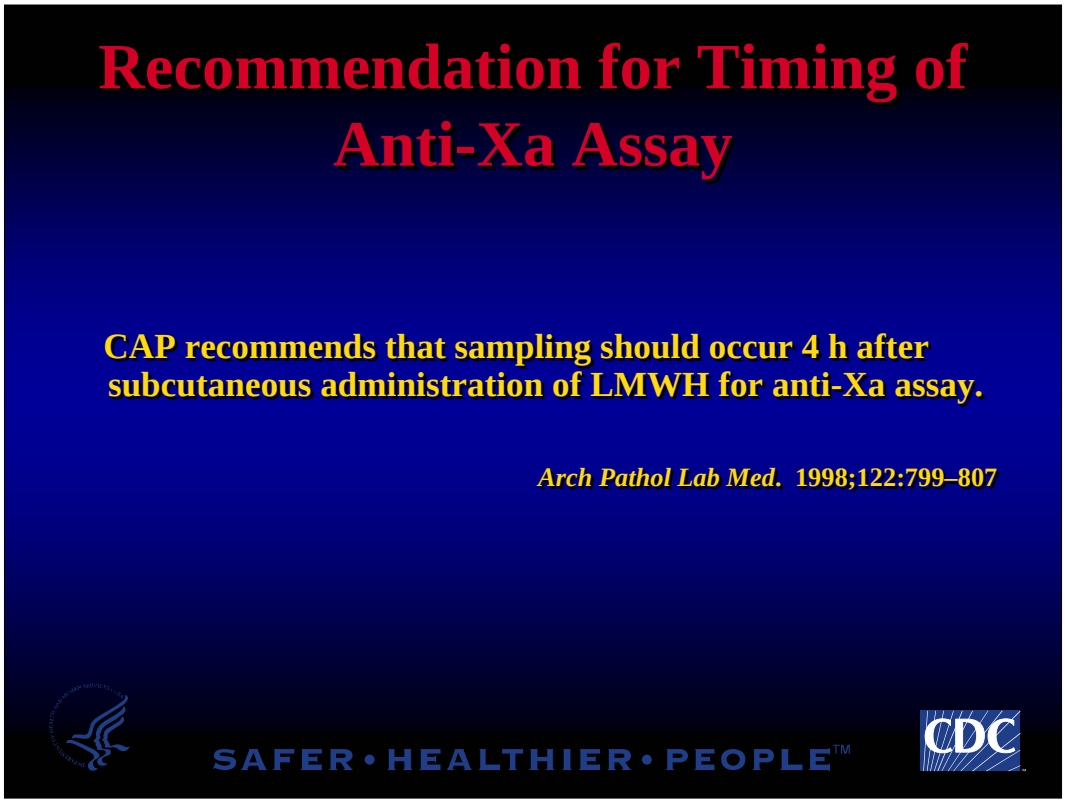
Contrary to accepted laboratory practice, ¼ of the respondents reported using unfractionated, as opposed to low molecular weight, heparin as a calibrator for anti-Xa assay; and another ¼ reported using heparinoid or other calibrators.



CAP recommends that laboratories use different calibrations for low molecular weight and unfractionated heparin and that they establish calibration curves for each lot and type of low molecular weight heparin. In agreement with these recommendations …



… 3/4 of the respondents reported using different calibration curves for low molecular weight and unfractionated heparin, and ~40% reported using different calibration curves for each type of low molecular weight heparin.



CAP recommends that sampling for anti-Xa assay occur 4 hours after subcutaneous administration of low molecular weight heparin. In agreement with this recommendation …

Timing of Anti-Xa Assay

Time of specimen collection after subcutaneous administration of LMWH	No. (Proportion)
Our coagulation laboratory does not recommend a time for testing	17 (46%)
4 h after injection	12 (32%)
2—4 h after injection	5 (14%)
Do not know	2 (5%)
≥5 h or more after injection	1 (3%)
Others	0

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… ~30% of the respondents noted they collected specimen for anti-Xa assay 4 hours after injection of low molecular weight heparin, while ~50% of the respondents reported that they did not recommend a time for testing of anti-Xa assay.

Most Commonly Performed Coagulation Tests

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Most Commonly Performed Coagulation Tests

Test	No. (%) of large hospitals	No. (%) of small hospitals	*P*
PT	310 (100%)	295 (100%)	1.000
aPTT	309 (99%)	292 (98%)	0.229
Bleeding time	277 (89%)	270 (90%)	0.699
Fibrinogen	295 (95%)	163 (59%)	< 0.001
D-dimer	252 (83%)	124 (46%)	< 0.001
Fibrin(ogen) degradation products	200 (67%)	92 (35%)	< 0.001
Activated clotting time	170 (58%)	70 (27%)	< 0.001
Thrombin time	159 (54%)	50 (19%)	< 0.001

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This slide shows the top 8 most commonly performed coagulation tests, as reported, in the order of decreasing use. Except for the top 3 tests—PT, aPTT and bleeding time—significantly greater proportions of the large hospitals performed each of these and the other 20 coagulation tests we examined.

Concluding Remarks

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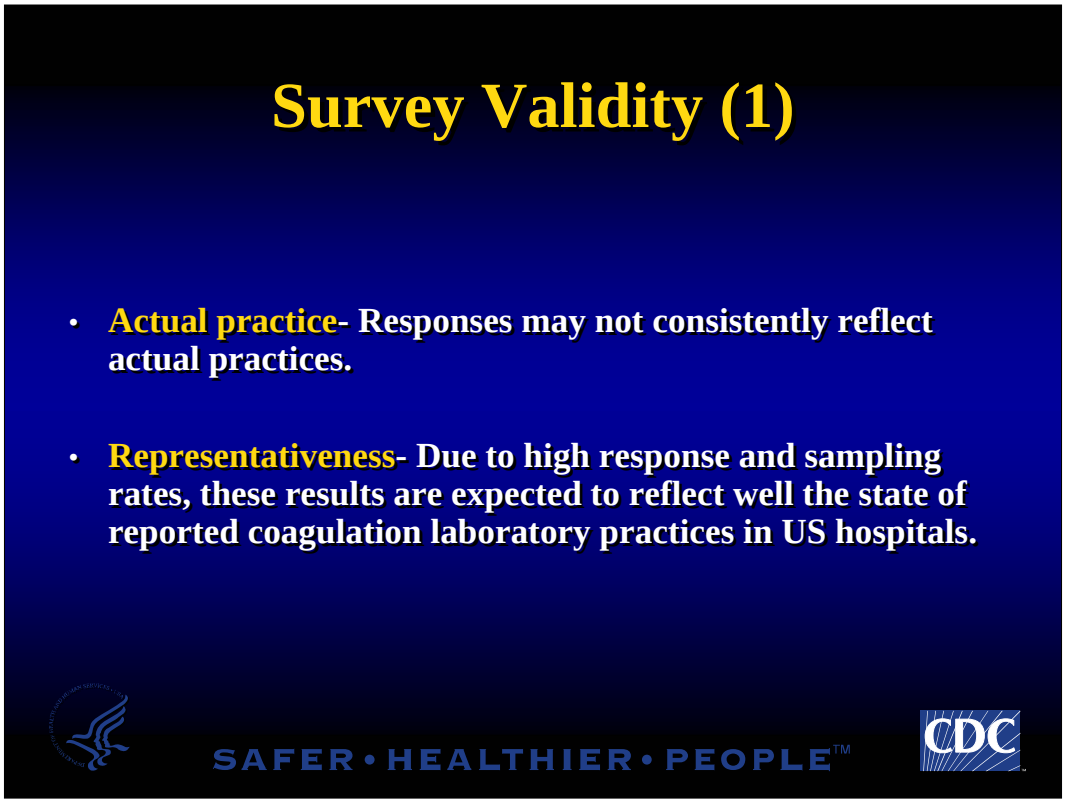
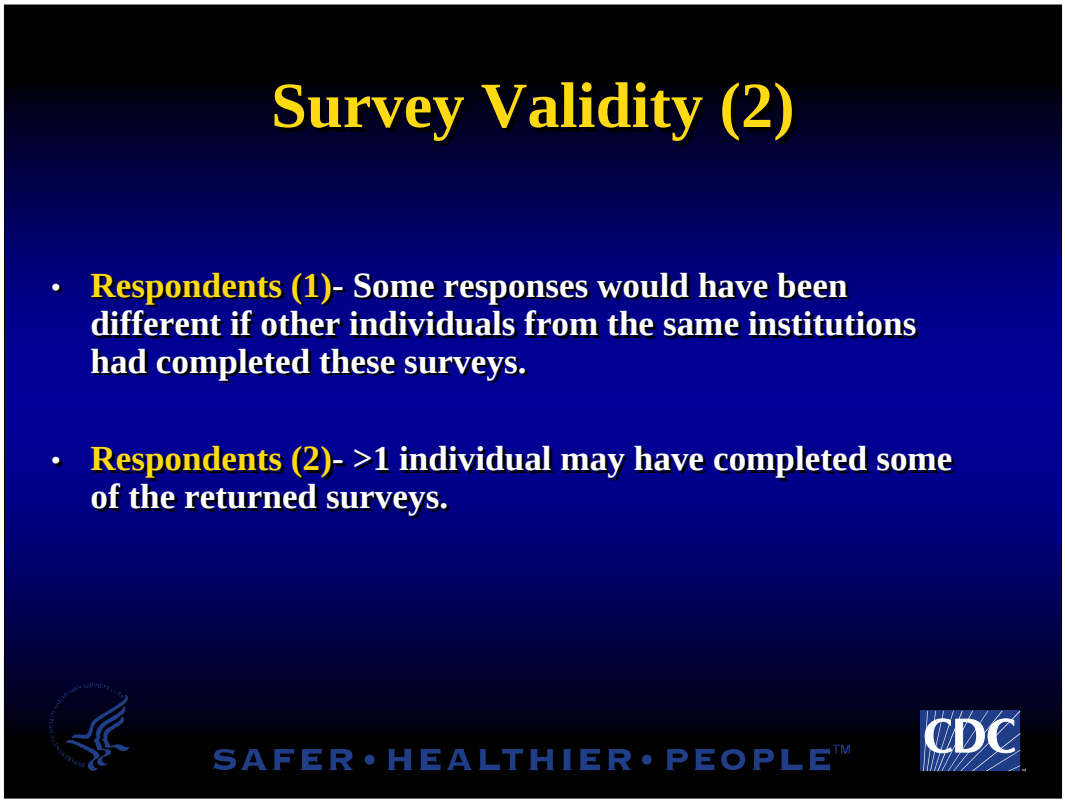
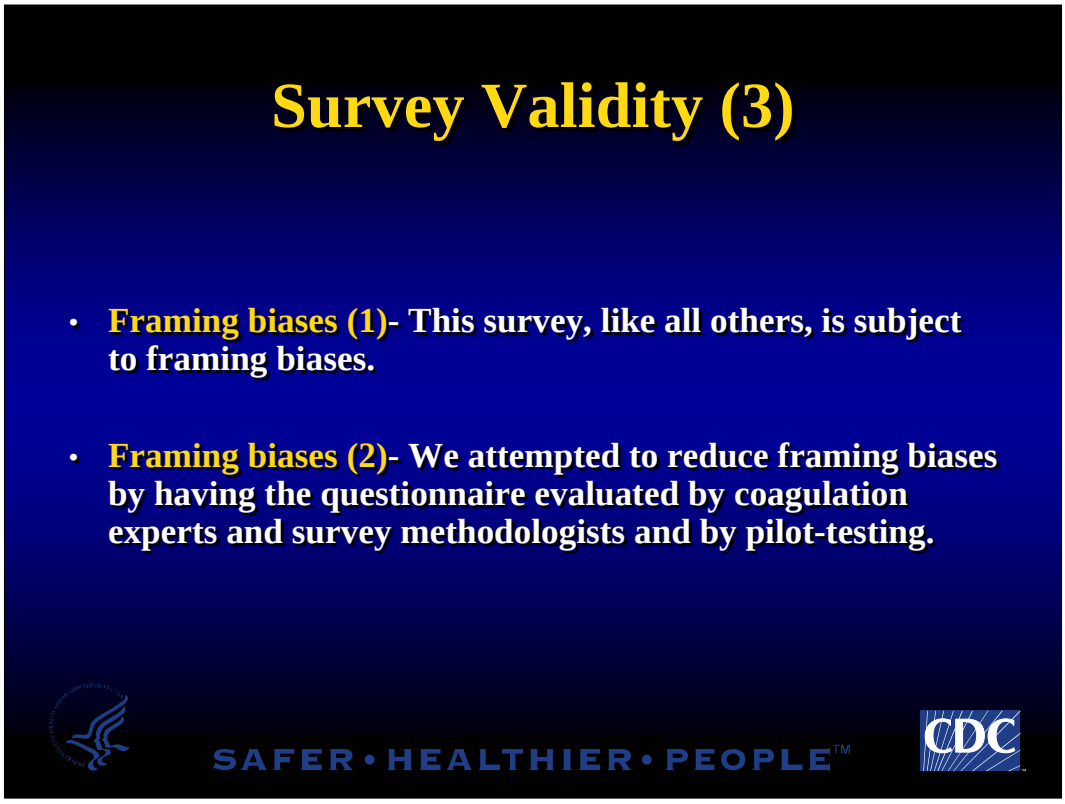


An inherent limitation of this and any other survey is that responses may not consistently reflect actual practices.

Because of the high response and sampling rates, this survey is expected to reflect well the state of reported coagulation laboratory practices in US hospitals in 2001.

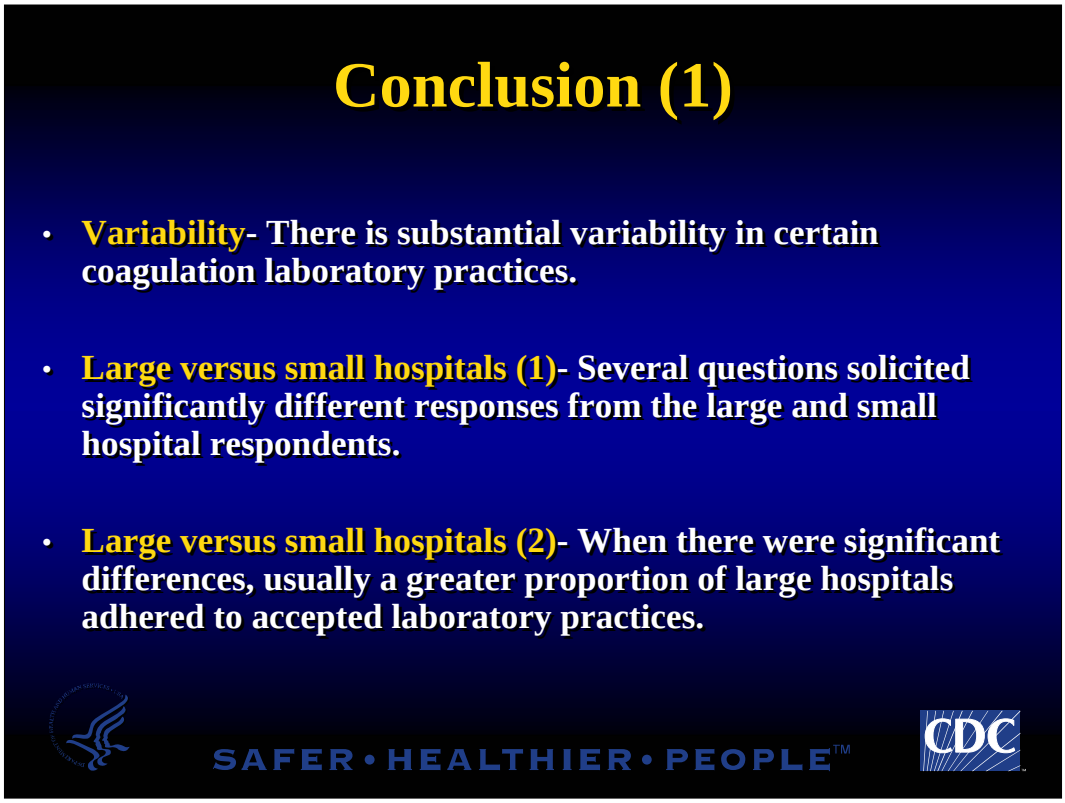


We didn't capture data on the actual individual or individuals responding at each hospital, and we also did not devise any mechanisms—for practical reasons—to assess intra- and inter-respondent reliabilities within the same institution.



Like any other survey, this questionnaire is subject to framing biases. We did attempt to reduce these biases by having the instrument evaluated by survey methodologists and coagulation experts as well as by testing versions of the survey by 9 hospital coagulation laboratories.

We excluded from the sampling frame the hospitals participating in pilot testing and also the hospitals of the coagulation experts consulting us in the development of this survey.

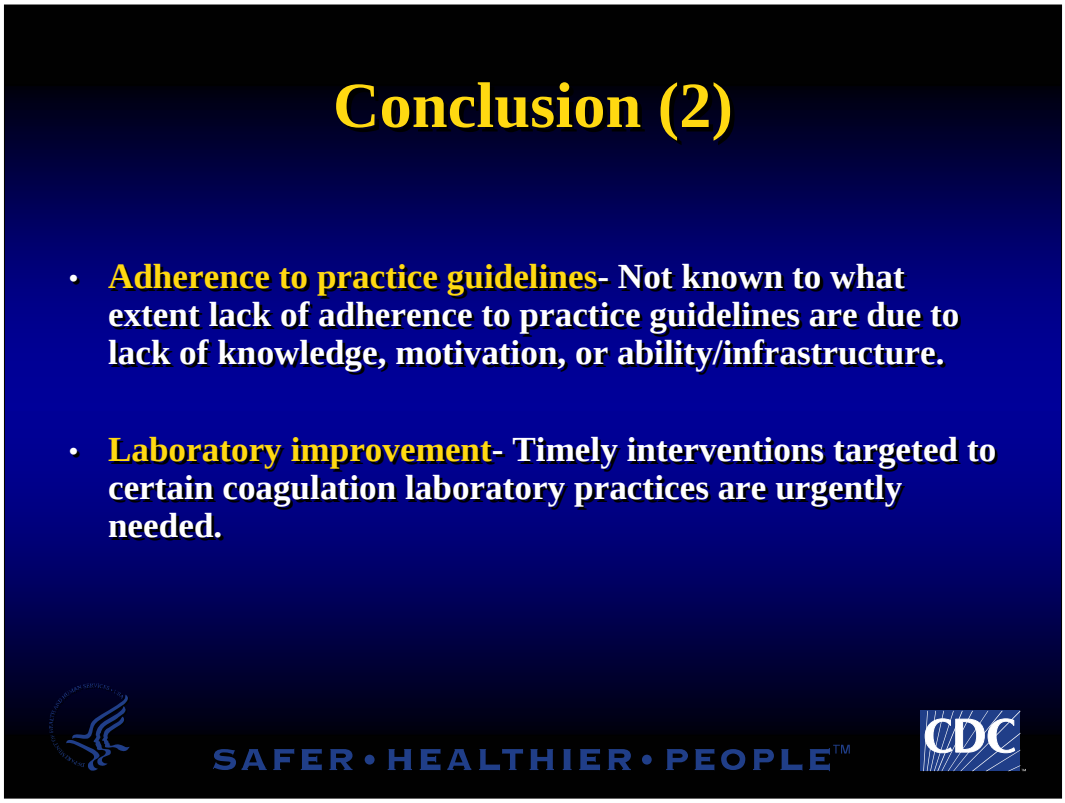


In conclusion …

This survey showed that there were substantial variabilities in certain coagulation laboratory practices.

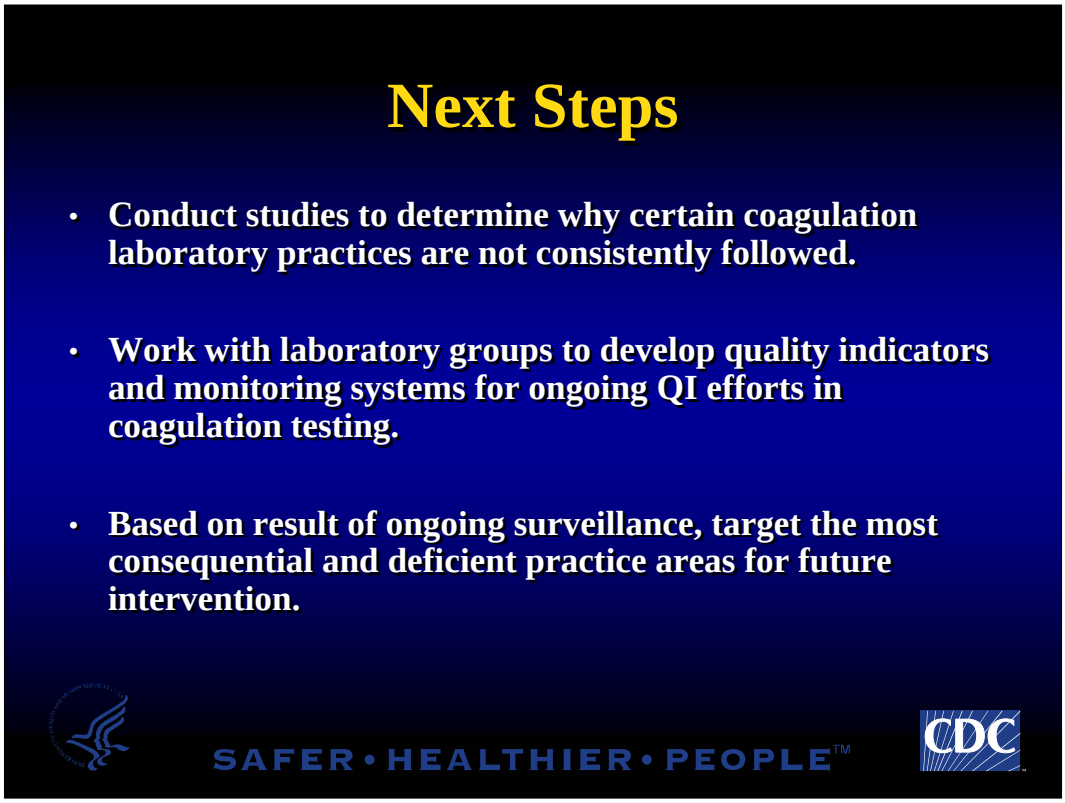
Although in most cases, response patterns from the large and small hospital respondents were not significantly different, several questions solicited significantly different responses from these 2 groups.

When there were significant differences, usually a greater proportion of the large hospitals adhered to published laboratory practice recommendations and guidelines.



We don't know to what extent not following practice recommendations and guidelines are due to lack of knowledge, motivation or ability.

Based on these data, timely interventions targeted for improvement of certain coagulation laboratory practices are urgently needed.



Where should we go from here?

We should conduct studies to understand why certain coagulation laboratory practices are not consistently followed;

We should work with laboratory groups to develop quality indicators and monitoring systems for ongoing quality improvement efforts in coagulation testing; and

We should target the most consequential and deficient practice areas for future intervention. These efforts should include dissemination of practice guidelines and administration of periodic surveys to assess and lead changes in practice patterns over time.

Acknowledgment

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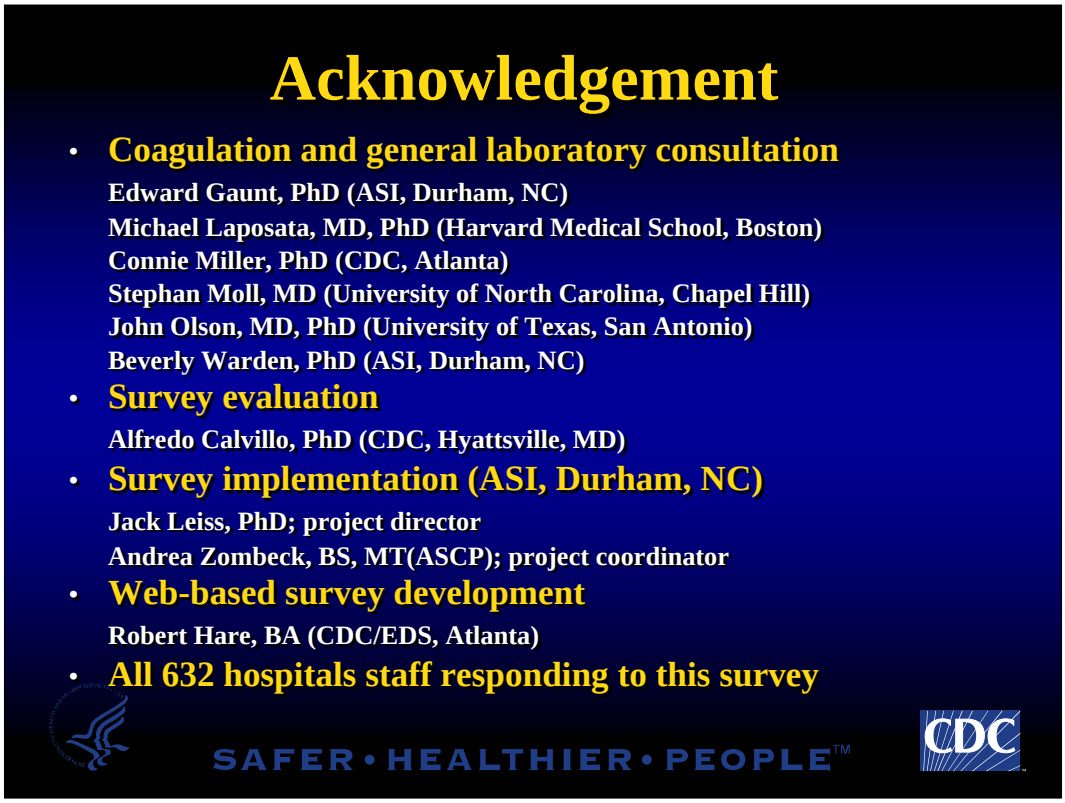

This survey would not have been possible had it not been for the contributions of numerous colleagues, many of whom are not listed in this limited space; and I would like to take this opportunity to sincerely thank all those who have been involved at various stages of this study.

Finally, I want to thank you for your attention and for your interest.

You can download the report of this survey at this URL. This site went live 2 days ago.

Now, I am pleased to take the 1st question.