The annual AABB conference: balancing patient safety and cost-effectiveness

The AABB – formerly known as the American Association of Blood Banks – held its annual meeting in New Orleans, Louisiana, in October. The conference indicates that the sector is in rude health despite the recession, write Kerri Weinert, Andrew Demeusy, and Ji Shi of Boston Biomedical Consultants

At this year's AABB conference, attendance was down by roughly 13% compared with an average of around 7,000 delegates in recent years, though approximately 200 exhibitors attended, and discussion was directed towards coping with the economic downturn. A focus on the organisation's ability to continue the mission of stewardship of the blood supply resulted in higher levels of interest in appropriate use, productivity, and inventory management.

Delegates at the AABB's annual meeting have a significant interest in new in vitro diagnostic (IVD) products and emerging technologies, as well as improvements to existing systems and the immediate influences of the external environment. New IVD systems were seen from companies including Immucor, which launched its fourth-generation automated blood grouping and typing system, the Galileo Neo, and Bio-Rad, which exhibited its new system, the IH-1000 (intended initially for the international market). Just before the meeting, Bio-Rad had announced that it had signed an agreement to purchase certain diagnostic businesses from Biotest, including its blood grouping and typing business.

The Research and Progress sessions, which serve as a forum for topical discussion and debate, reappeared this year after absence in previous years. They covered topics including molecular-based blood grouping and typing and selective infectious disease testing strategies. Finally, the convention hosted a much anticipated update chronicling the experience from the first pilot sites participating in the US Hemovigilance Program, a scheme designed to track adverse events associated with blood transfusion.

It appears that in 2009, blood donation activity in the US was slightly down on 2008 for the American Red Cross (ARC), and unchanged for independent blood centres. This was partly ascribed to the economic downturn causing a decline in elective surgical procedures, and thus demand for blood products. The ARC has seen a decline of 3% in the number of blood donors scheduling appointments and giving blood; however, it is difficult to attribute this decline to one single factor. Although there has been a reduction in demand for blood products over the past six months or so, the demand for plasma donations increased again in the US as demand for fractionated products continues on a global basis.

Automation for NAT

A significant focus at AABB was automation for nucleic acid-based testing (NAT) and associated multiplex testing. Both Novartis (formerly Chiron) and Roche focused on expanded menus for their current automation platforms. Novartis displayed its Procleix Tigris instrument and promoted its fully FDA-approved Procleix Ultrio assay, marketed for detection of HIV-1, hepatitis B virus (HBV) and hepatitis C virus (HCV). Although the company received full FDA approval in August 2008 (the initial approval lacked the HBV screening claim), the ARC continued its own post-marketing study throughout the remainder of 2008 and into early 2009. The ARC released results from its study in early 2009, and in April 2009 both the ARC and America's Blood Centres (ABC) signed multi-year contracts for the Procleix Ultrio assay. Novartis CE marked the Procleix Ultrio Plus assay, which is designed to provide greater HBV sensitivity compared to the Procleix Ultrio, in mid-2009, immediately making it available in selected countries.

Novartis did not, however, promote its next-generation automated Panther system, which is currently in late stage development by Gen-Probe. A revised collaboration agreement with Gen-Probe was inked in January 2009. Gen-Probe has also stated that it may develop tests for regional diseases such as the dengue and chikungunya viruses.

Roche highlighted the cobas s 201 system, its modular real time automated PCR platform, and cobas TaqScreen assays. Although the company continued to promote its cobas TaqScreen WNV assay for West Nile virus, of higher importance was the cobas TaqScreen MPX assay for multiplex detection of HIV-1 Group O, HIV-1 Group M, HIV-2, HCV, and HBV. This received FDA approval in December 2008 and has been available in Europe since early 2006. The cobas TaqScreen DPX test, currently in late stage development for qualitative identification of hepatitis A virus (HAV) and quantitative detection of parvovirus B19, was promoted through abstracts and at the company's corporate symposium. Further out, Roche continues to assess opportunities for the development of tests for emerging pathogens, and is also likely to focus on dengue and chikungunya initially. A next-generation cobas TaqScreen MPX assay which will provide immediate discriminatory results is currently in development along with next-generation automation; however, neither product was a promotional strategy for the company.

In early April 2009, the FDA's Blood Products Advisory Committee (BPAC) held a much-anticipated meeting in which HBV NAT was discussed. There is controversy over the adoption of HBV NAT as part of new FDA-approved multiplex tests from Chiron and Roche in relation to higher pricing, lack of FDA mandate, and clinical utility. After presentation of data on the ability of HBV NAT to detect donors with window period or apparent vaccine breakthrough infections, the BPAC voted in agreement with the FDA's position to presume that these units are infectious pending further studies. In a joint statement with the ARC, AABB stated that adopting HBV NAT will provide an "incremental improvement in HBV transfusion safety…from donors with acute infection whether previously vaccinated or naive."

In assessing HBV NAT for donors of human cell and tissue-based products (HCT/Ps), BPAC indicated that it was appropriate to use minipool testing for living donors if p14 ▶

the package insert included this clearance, but it may not be suitable for nonheart-beating donor specimens. Although HBV NAT is not mandated by the FDA, both the ARC and ABC in the US have moved to adopt the assay as studies have detected several case of yield and centres continue to strive for the safest blood possible. The ARC conversion is expected to be complete by early 2010; however, due to the fragmented nature of the ABC, the adoption rate will be much slower and some centres may choose not to adopt the assay. Certain Roche customers have been using the cobas AmpliScreen HBV test since 2003. Novartis has indicated that pricing has been a hindrance to adoption as centres weigh the incremental cost with incremental safety provided. Of note, the transient increase in circulating HBV particles following immunisation is still a phenomenon as it is unknown if such individuals are capable of transmitting HBV infection. To date, there have been no reports of such transmissions while vaccinations continue to increase.

Blood grouping automation and test products

With no new products unveiled last year, the activity among several key companies this year was noteworthy, and the appearance of a new company, Quotient Biodiagnostics, offering a complete line of blood grouping and typing (BGT) reagents – a welcome addition to the market voiced by many customers.

The announced mergers in this area, namely the Bio-Rad acquisition of Biotest Diagnostics, a significant portion of which is BGT systems and a full reagent line (some tests are still awaiting FDA approval), were certainly of interest. However, attendees were left to speculate about the future, given that neither company could comment on the transaction. Also a consequence of merger activity in 2009, the Olympus PK 7300, an ultra high-volume automated BGT system, was displayed in the Beckman Coulter booth. Beckman Coulter is the new owner of the diagnostic business, following closure of the transaction in the third quarter.

In the new systems area, there was high interest and traffic in the Immucor booth with the first public display of the new fourth-generation Galileo Neo, a fully automated blood bank instrument. Like the original Galileo, Neo is designed for the high-volume transfusion service and blood donor centre laboratory. Neo incorporates many of the same features seen in the Galileo, but includes hardware and software upgrades that provide enhanced functionality such as STAT priority testing, decreased turnaround times, more flexibility in resource handling and lower maintenance – all designed to provide improved workflow to high-volume laboratories. The instrument will feature the following specifications:

- Highest type and screen throughput in the market, at over 60 type/screens per hour
- Capacity for 224 samples; continuous feed using linear racks
- Capacity for 15 microplates
- Comprehensive process control strategy (daily quality control using pre-manufactured QC kits)
- Touchscreen user interface with Windows-based software
- Reflex testing (unique for this product class)
- Bi-directional interface
- Remote diagnostics (unique for this product class)
- Floor model instrument with the same footprint as the Galileo, but slightly taller.

Like the Galileo and the Galileo Echo, the Neo will use haemagglutination for blood typing and phenotyping assays (and donor re-typing) and Immucor's patented Capture solid phase assays for antibody screening, antibody identification, Weak D, direct antiglobulin tests, IgG crossmatch and cytomegalovirus. An improved control strategy for the three-cell antibody screen assay makes Neo a more compatible instrument for laboratories that use the Galileo Echo as a backup instrument.

Immucor expects to release the Neo in Europe within the next 90 days and is scheduling an FDA submission for the end of 2010. Immucor also promoted its continued rollout of the Galileo Echo, which received approval in June 2007.

The second new automated BGT system, also for high-volume testing, shown for the first time in the US, was the IH-1000 system from Bio-Rad (DiaMed) which utilises the current ID-Cards manufactured by DiaMed and sold outside the US. This floor model system is designed to offer a maximum throughput of up to 720 tests per hour.

Ortho-Clinical Diagnostics (OCD) displayed its current automation (individual models available in the US and for the international markets) and launched the new FETALSCREEN II Fetal Maternal Hemorrhage Screening Test, a manual qualitative test that detects D (Rh)-positive foetal red blood cells in the maternal circulation of pregnant Rh-negative women. OCD also "previewed" its new Remote Monitoring Centre (RMC), an innovative instrument service option launched in July 2009 and currently available to OCD's core laboratory customers for routine diagnostic testing. The RMC, using proprietary remote diagnostic software tools, continuously tracks the condition of laboratory instrument performance on a remote basis. It is designed to detect and predict potential instrument problems before they take place, in order to maximise system up time, while further ensuring reliable test results. OCD intends to make the RMC available to customers using their systems for BGT and donor screening for viral infections in the future; a timeline was not specified.

The newest entrant in the BGT market, Quotient promoted the October 2009 FDA approval of its first 15 tests. Quotient was formed earlier this year to directly commercialise its line of products under the trade name ALBAclone. The tests approved under this first BLA include products used in forward blood typing and rare anti-sera (all are monoclonal antibody based). Quotient also plans to make additional tests available in the future including red cells for reverse typing and antibody screening and identification, among others. The company does not plan to sell a conventional automated BGT system in the near term.

Molecular blood grouping and typing

Currently, the only company with a US commercial presence – though its products are still only sold on a research-use-only basis – in the molecular BGT technology segment is Immucor, through its March 2008 acquisition of BioArray Solutions. Internationally, the Progenika BLOODChip was developed by the Bloodgen consortium and is a microarray-based test that determines the main allelic variants in blood groups ABO, RhD, RhCE, Kell, Kidd, Duffy, MNS, Diego, Dombrock and Colton, and 12 platelet antigens as the result of the analysis of 128 polymorphisms.

The primary advantages of molecular genotyping over serological testing are that it is automatable and is capable of detecting weakly reactive variants; however, this is countered by a number of disadvantages such as cost and the inability to detect unknown variants. Historically, the standard has been to operate in a "Phen2Gen" mode where genotyping is only performed on unusual serological phenotypes; however, as sequencing becomes more common, the industry is beginning to see a switch to "Gen2Phen" where genotyping is performed and used to help predict and understand a phenotype.

At AABB 2009, the BioArray BeadChip products were promoted within the Immucor booth as the acquisition of the company in 2008 had been completed. The company currently has more than 35 active installations within the US, with each site performing over 75,000 tests per annum; internationally, the company has more than 10 active sites. The BeadChip

system is based on microparticle bead technology on a semiconductor wafer. To summarise the technology and workflow, DNA must first be extracted, amplified using multiplex PCR, and discriminated (selecting single-stranded DNA). The clean DNA is then hybridised to the BeadChip array which is spotted with microparticles tagged with target-specific probes. The array is then incubated to allow for probe extension prior to detection and analysis. Total processing time is approximately five hours and is currently not automated; however, the company is working on "walk-away" sample extraction. As a leader in this emerging area, the technology was well represented with the abstract presentations and workshop sessions.

Adoption of molecular BGT is slowly increasing as more laboratories see its advantages over traditional BGT technology. Several interactive sessions at the meeting addressed this, including a session entitled "Molecular Immunohematology", chaired by Bill Flegel. Dr Flegel is a transfusion medicine specialist who has a long history as a key opinion leader in this area, from more than 15 years at the German Red Cross Blood Centre in Ulm, Germany, before moving to the US in spring 2009. From the opening line: "Molecular techniques have arrived at the doorsteps of the blood group serology laboratory," turnout for the session was high and featured several speakers with significant experience in the area, including Connie Westhoff of the ARC, Gregory Denomme of BloodCentre of Wisconsin and Wendy Paul of Children's National Medical Centre in Washington, DC, among other noteworthy speakers. Molecular BGT is poised to make gains in patient testing, donor-recipient matching, and transfusion support for sickle cell disease.

Also noteworthy was a symposium titled, "Establishing a Genotyping Lab in Your Institution" in which both manufacturers and blood centres presented on the technologies available and provided practical guidance for those attempting to bring molecular BGT in-house. A presentation by Brad Pietz of BloodCentre of Wisconsin, discussing his experiences using the BioTrove OpenArray technology for red blood cell and platelet antigen genotyping was of particular interest to attendees. Having proved the concept, the centre is developing a high-throughput process using this technology including analysis and management of the huge amount of data generated. Currently, the bottleneck is the DNA extraction but the centre is looking to implement automation.

Automation for immunoassays

There were no new immunoassay-related testing systems for virology screening this year. In September 2009, though, Abbott announced FDA approval of the Abbott Prism HIV O Plus test, as it predicted would take place at last year's meeting. This test approval brings the menu to five tests, with the next expected assay the Abbott Prism Chagas test and the Chagas confirmatory immunoblot assay. Both continue to progress in the clinical testing phase and are expected to launch in 2010. On the instrument side, Abbott also promoted the features of the current Prism with the Prism nEXT instrument upgrade, which has been released outside the US. The Prism nEXT software builds on the features/benefits of the current Windows XP-based Architect series software.

OCD displayed the new Ortho Verseia Pipetter, first introduced at last year's conference. It is intended for use in pipetting virology tests supplied by OCD for donor screening, as part of the Ortho Summit System (OSS). The system was FDA cleared in May 2009; further assay migrations and FDA submissions will occur in 2010, with a target launch date at the end of 2010 with HCV, Chagas, HIV O, and HBsAg assay availability.

Emerging analytes

The need for immunoassay-based screening for new pathogens that may pose a risk to the US blood supply was evaluated in several sessions including one called "Selective Infectious Disease Testing Strategies". Various other sessions on emerging analytes were chaired by Drs Roger Dodd and Louis Katz.

Trypanosoma cruzi, the aetiological agent of Chagas disease, is endemic in parts of Mexico and Central and South America. In early 2007, blood centres in the US implemented universal screening for antibodies to *T cruzi*; however, retrospective studies have indicated a lower than expected number of transmissions and have shown that most cases of donor infection are associated with birth or prolonged residence in Latin America. In response, in mid-2009 some US blood centres, including ARC, implemented selective testing, focusing on one-time testing to screen the donor. Studies looking at the possibility of using a questionnaire to screen for high-risk donors have proved unreliable.

The economic impact of this move was much discussed, given that the test manufacturer of the *T cruzi* antibody assay has countered the decline in test volume with price increases, partially offsetting the value to the blood centre. In an environment where resources are limited, risk evaluation in some cases is shifting. "The concept of uniform infectious disease testing of donors, whether or not they have been tested in the past, has been the paradigm up until now. But there has emerged a willingness to look at other approaches, such as confining screening to testing donors on a single occasion or to testing in selected regions of the US based on the geographic distribution of a particular infectious disease agent," said Dr Steven Kleinman, the president of Victoria, Canada-based Kleinman Biomedical Research.

Similar to prior AABB meetings, other infectious agents such as babesia, chikungunya, and dengue were widely discussed as outbreaks of the latter two continue to increase in frequency and global distribution. Although emerging pathogens are viewed as an under-recognised problem, documented transfusion transmission is uncommon. Along these lines, the four-year AABB Transfusion Transmitted Diseases Emerging Infectious Disease (EID) Project has worked to monitor and prioritise emerging infectious disease agents for which transfusion/transplant transmission is documented or potentially exists and there is no effective intervention. In August 2009, the group published a special supplement on EID agents in the journal *Transfusion*, providing tools to identify, describe, and prioritise EID agents.

TRALI

Transfusion related acute lung injury (TRALI) discussions continued, but were focused on the effectiveness of measures taken to reduce the number of TRALI cases. In 2006, the AABB recommended that blood centres take steps to address TRALI; however, no specific steps were recommended. A large percentage of the blood centres opted to move to predominantly male plasma, or its equivalent, and data from the US FDA, the UK and Germany indicate that this move has been effective in reducing risk. This approach is not practical for platelet apheresis, but a possible alternative approach is to screen donors for leukocyte antibodies. Although research has implicated human leukocyte antigen (HLA) and human neutrophil antigen (HNA) antibodies in TRALI, fewer than 50% of blood centres in the US are currently performing HLA testing and none are routinely performing HNA testing. A follow-up to a previous HLA donor prevalence study, LAPS II, is tracking platelets and plasma from HLA-positive donors to see if recipients develop TRALI; data collection will continue through the end of 2009 with results expected in 2010. HLA and HNA product companies GTI, One Lambda, and Gen-Probe/Tepnel continued to exhibit at AABB this year, but did not have a dominant presence.

GTI Diagnostics promoted its DonorScreen-HLA product for use on the QUICKSTEP Automated ELISA platform, which received FDA approval in August 2008, and the Red Cell EZ Type kits for allele-specific amplification (for research use p16 ▶

only). The Red Cell EZ Type kits employ pre-cast E-gel packs to perform RBC molecular typing with sequence specific primers. The company hosted two educational events to address recent advances in platelet testing and the need for platelet typing and antibody analysis, specifically reviewing the company's new PAK LX product in development. The PAK LX test is a Luminex-based assay for the detection of HPA and HLA antibodies. The company has completed its clinical trial and is working towards submitting the assay to the FDA. One Lambda promoted its Luminex-based LABXpress system and LABScreen Multi products to screen for HLA and HNA antibodies. The LABXpress system automates the sample preparation process and allows processing of up to 800 samples in eight hours.

Platelet bacterial contamination

Bacterial contamination remained a key topic at AABB 2009 with the main focus on point-of-issue tests and pathogen reduction/inactivation. Verax promoted its Platelet PGD test in its booth and at a company-sponsored workshop. The company received FDA approval for use with leukoreduced apheresis platelets in September 2007 and submitted data for a release claim to the FDA in early 2009; the test was CE marked in September 2008. On November 17 2009, Fenwal, the exclusive global distributor, announced that the Verax Platelet PGD test had received FDA clearance as a quality control test in whole blood-derived, pooled platelets prior to transfusion. The test takes approximately 30 minutes to perform and now has clearance for both pooled and single-donor platelets.

Pall promoted its Leukotrap Synergy platform, composed of the Leukotrap RC System with RC2D Filter, Acrodose Plus System, and eBDS System. This platform is intended to provide leukoreduced red cells along with the platelets, allowing for the pooling of up to six individual platelet units, and plasma components, improving product availability. The company sponsored an industry workshop where several blood centres presented how they have successfully implemented the Pall systems to meet their operational and financial goals. Similar to prior years, Immunetics promoted its BacTx kits for detecting bacterial contamination of platelets; kits are currently for research only.

Pathogen reduction/inactivation

Bucking the trend, pathogen reduction/inactivation received less coverage this year compared to the 2008 meeting. Caridian BCT and Cerus continue to develop technologies for pathogen reduction, the latter of which held a corporate workshop to review its Intercept Blood System and US SPRINT study (a Phase III clinical study with apheresis platelets). The SPRINT trial enrolled 645 patients and met its primary endpoint of the proportion of patients with Grade 2 bleeding; however, in mid-November 2009, the FDA expressed concerns regarding observed differences between the test and control arms, and indicated that it would need additional data for a PMA application. Cerus plans to perform a new randomised, double-blind, non-inferiority trial to address the concerns regarding haemostatic efficacy and safety. In April 2009, Caridian BCT launched its three-component protocol for its Atreus Whole Blood Processing System in Europe. This separates a unit of whole blood into an RBC unit, a plasma unit, and a platelet unit suitable for pooling.

US Biovigilance Network: a public/private collaboration

A series of presentations on the US Biovigilance Network, covering the user experience of four institutions in the US (out of the nine that agreed to pilot the programme before it goes live in 2010) were featured at the meeting. In May 2009, nine medical centres across the US participated in the pilot programme to collect data to track adverse reactions experienced by patients undergoing blood transfusions and adverse events associated with transfusion.

This is the first information to have been released on the progress of and experience with the US Biovigilance Network, a collaboration initiated in 2006 between the federal government (the CDC) and organisations involved in transfusion medicine. The AABB continues to secure funding for the programme, but the CDC's programme (surveillance systems) will continue regardless of the funding outcome. Other potential benefits of the system were noted by Jim MacPherson, CEO of America's Blood Centres. "The Biovigilance Network will be a good monitor to answer questions like breakthrough HBV infections or phase IV trials of new blood products. Lack of evidence of transmission can drive policy if you are confident in your monitoring system," he said.

Questions to the pilot sites included "What impact has the pilot study made on improving patient outcomes and safety, or when do you foresee an impact?" and "Did the capabilities, or what you believe to be the future capabilities, of the system meet your expectations?" The comments, including one from a very large institution, were quite positive. Dr Katharine Downes, of University Hospitals Case Medical Centre in Cleveland, said: "We have under 12 months of data so it is really too soon to assess change in patient outcomes, but it has made a positive impact on our operations. The software met our expectations. Moreover, it is very flexible." Dr Louis Katz also praised the flexibility of the software, but noted: "Consistency of surveillance and application of definitions which have been validated is critical, and will be essential if we are to compare like institutions and like events, which will be invaluable."

During the conference, the incoming President of AABB, Jackie Fredrick, shared her goals and priorities for the coming year, stating that Biovigilance will be a priority because it will not only improve the safety of donors, patients, and the blood supply but also is an exceptional model to show how one can use evidence-based medicine in this country to lower health care costs and improve safety and quality.

The list of hospitals that have committed to joining the collaboration continues to grow (see www.aabb.org/Content/Newsletters_and_Journal/Biovigilance_Update for the current list). The US experience will be watched closely by the international organisations that have maintained (and benefited from) such activity for years to see if any new US-based initiatives could translate into better patient care in their institutions.

Dr Barbee Whitaker of AABB who (among others) has taken on a major role in the co-ordination and implementation of the US Biovigilance Network since its inception, said: "We are very excited to kick off the programme in January 2010 and we believe that, of the list of institutions that have made a commitment to implement the programme, upwards of 50 sites could be initial users. As to reporting back aggregate data from the user group, this will take at least 12 months of data collection, so a report in the fall 2011 timeframe is anticipated."

The CDC and AABB formed this public-private partnership to develop a haemovigilance surveillance system based on the CDC's existing surveillance systems. The backbone of the biovigilance data collection programme is the CDC-developed National Healthcare Safety Network (NHSN), a component of which has been used for data collection on nosocomial infections for years.

To further educate prospective hospitals on the system, live demonstrations of the recipient modules of the NHSN and the donor haemovigilance system were held in the Biovigilance Pavilion, which was located in AABB's Member Action Centre. Attendees had the opportunity to see how data are input into the modules, view the system requirements and discuss the adverse event definitions.

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