Davies Award of Excellence Case Study

Program Year 2023

Development of A Comprehensive Intelligent Anti-Microbial System: An Epochal, Fast, and Digitally Precise Prediction of Therapeutic Antibiotics

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Executive Summary

Early treatment with an effective antimicrobial agent is critical to the outcome of an infected patient. Sepsis impacts and causes millions of deaths annually worldwide, including Taiwan, resulting in mortality rates of up to 29.2%. Microbial diagnosis at the Center of Laboratory Medicine is the beginning of our efforts. However, the critical condition changed more rapidly than that of the traditional method for identifying pathogens and antimicrobial susceptibility.
To accelerate sepsis diagnosis, China Medical University Hospital (CMUH)develops a comprehensive antimicrobial artificial intelligence (AI) platform, the Comprehensive Intelligent Anti-Microbial System (iAMS), which provides personalized antibiogram, sepsis and mortality risk prediction and monitoring, multidrug-resistant organisms (MDRO) detection/prediction, and intelligent antibiotic clinical decision support systems. Under limited clinical capacity, AI can improve medical efficiency. The number of usage statistics has reached 62,179 within one year and is currently increasing. After the system was launched, the mortality rate due to sepsis was successfully reduced. The mortality rate decreased by 7.1% compared to 13.4% in the same quarter of 2020. Through this system, it is expected that early diagnosis and precision treatment can be provided as soon as possible to increase the survival rate.

Clinical Problem and Pre-Implementation Performance

The iAMS demonstrates significantly faster prediction times (**Table 1**) for accurately identifying and predicting outcomes related to carbapenem-resistant *Klebsiella pneumoniae* (CRKP)and methicillin-resistant *Staphylococcus aureus* (MRSA) infections (**Figure 1**). The platform is to compare the analysis of AI-predicted antibiotic resistance counts on the platform between 2021 and 2022.

Isolate	Method	Isolate number	Mean time (hr)
Carbapenem-resistant *Klebsiella pneumoniae*	iAMS	1786	39.8
	Traditional method		99.5

Methicillin-resistant *Staphylococcus aureus*	iAMS	1343	40.9
	Traditional method		106.4
Total	iAMS	3129	40.3
	Traditional method		102.4

Table 1. Comparison of time efficiency between AI predictive methods and traditional approaches

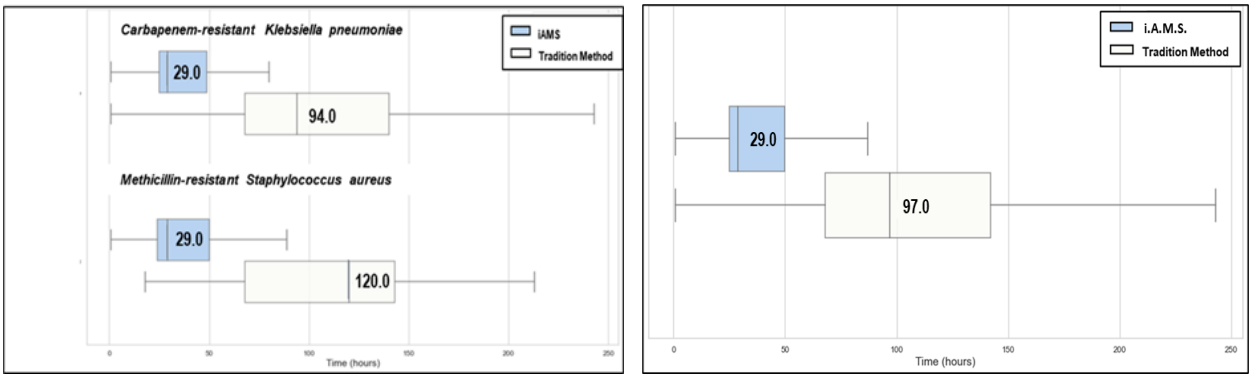


Figure 1. (a) CRKP and MRSA; (b)Total

Personalized antibiogram

Owing to the design of traditional electronic medical records (EMR), physicians often need to click on each microbiology report in the specific section in the EMR to read the culture reports and check out patients' microbiology species and their antimicrobial susceptibility. Especially for patients with a long history of infection, it would be inconvenient and time-consuming to search for a specific report and create infection-related records.

Sepsis and mortality risk prediction and monitoring

Sepsis is a clinical syndrome characterized by life-threatening organ dysfunction caused by a dysregulated response to infection. The clinical surveillance criteria proposed by Rhee (Rhee C, et al: Incidence and trends of sepsis in US hospitals using clinical vs claims data, 2009-2014. JAMA. 2017) was adopted as the gold standard for the definition of sepsis. This standard is based on two judgments: whether the patient is suspected of having an infection, and whether acute organ failure has occurred. The Sequential Organ Failure Assessment (SOFA) score is the main scale used to determine the extent of a patient's organ function or rate of failure. In addition to the SOFA score, there are other scores/scales for sepsis in use, such as qSOFA, MEWS, and SIRS, but they have an AUC of approximately 0.6 ~ 0.7 for diagnosing sepsis in all patients of suspected infection aged over 20 years. SOFA and such scales show high sensitivity to organ dysfunction, and a high probability of sepsis risk was also observed in patients with organ failure but not sepsis. Suspected infection is the most important criteria for

sepsis detection and mortality prediction, and patients age under 20 was excluded in the data used for developing the ML model (**Figure 2**).

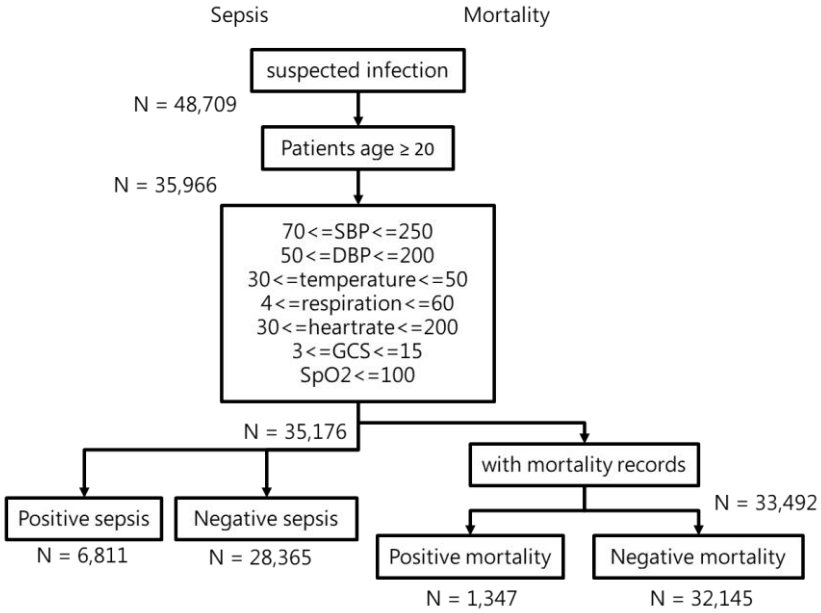


Figure 2. Dataflow of sepsis detection and mortality prediction

MDRO detection/prediction

Quick and accurate treatment with effective antimicrobial effects is critical for infected patients and can significantly influence the outcome after treatment. However, for precise antimicrobial therapy and dosage, the resistance profiles of presumed pathogens should be considered. Early confirmation of the infected microbial species can allow physicians to make targeted therapy decisions regarding various potential therapeutic options. Conventional methods usually require 12–24 h of sample culture and an additional 24–48 h to identify the bacterial species and conduct antibiotic susceptibility testing (AST).

Intelligent Antibiotic clinical decision support system

In previous research, 34.2% of 13,932 patients were prescribed inappropriate antibiotics, and this inappropriate or excessive use of antibiotics may increase the risk of antimicrobial resistance. Time is crucial, especially for saving lives from sepsis and infection. The main problem with antimicrobial resistance is that medical professionals cannot obtain sufficient diagnostic information quickly, and there are no comprehensive tools to assist them in deciding antimicrobials and their dosage. The information required may be stored in different systems and requires users to check in different windows.

Design and Implementation Model Practices and Governance

The integrated iAMS is constructed by a team of physicians specializing in infectious diseases and critical care medicine, Departments of Pharmacy and Information Technology, and

Centers of Laboratory Medicine, Big Data, AI, and AI innovation in CMUH, and is now fully integrated into the hospital information system (HIS) **(Figure 3)**.

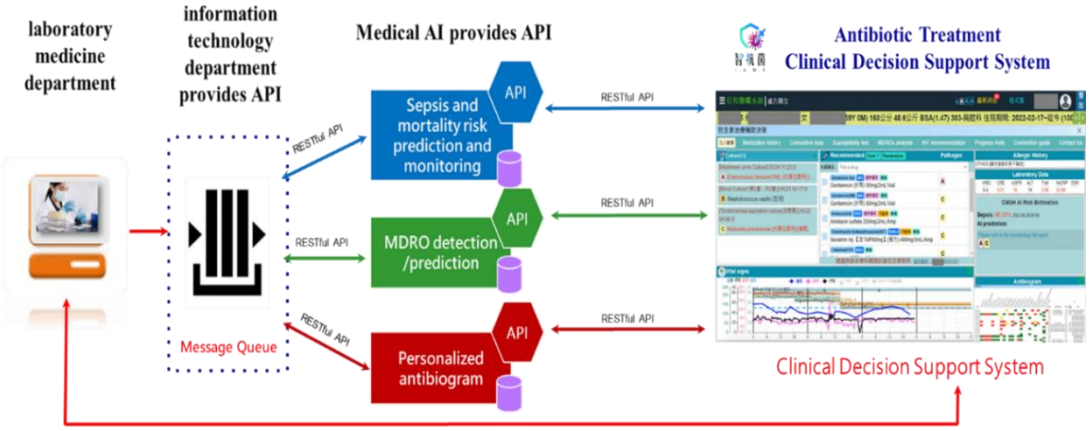


Figure 3. Key platforms in iAMS

Personalized antibiogram

The automatic integration of multiple microbiological reports and visualization of the susceptibility results can help physicians easily and correctly identify appropriate empirical antibiotics for treating the infection. This tool is especially helpful when the current culture results have not been finalized.

Design

The visualization design of the personalized antibiogram is not a brand-new design. It is adapted from the population-level antibiogram usually used to demonstrate the antimicrobial resistance epidemiology for antimicrobial stewardship in a hospital or within a region. At the population-level, the antibiogram shows the proportion of susceptible culture samples for each antibiotic and each bacterial. If the proportion of susceptible is lower than a certain threshold for a specific bacterium and a specific antibiotic, (i.e., only 50% susceptible), the antibiogram can be shown in red to warn the physicians that the local epidemiology suggests this bacterium is possibly resistant to that antibiotic. An example of published population-level antibiogram is shown in **Figure 4**.

In the personalized antibiogram of iAMS, the susceptibility results for each bacterial and for each antibiotic is shown in red if "resistant", in yellow if "intermediate", and in green if "susceptible" (**Figure 5**). The susceptibility is determined by the MIC value cutoffs in compliance with the current CLSI guideline. All information in the personalized antibiogram come from the microbiology reports. Therefore, the visualization should be intuitive to the physician who is familiar with a standardized microbiology report, which includes the bacterial name, antibiotic susceptibility results show in "S", "I", or 'R", and the original MIC values corresponding to the antibiotic susceptibility test. A similar design of personalized antibiogram has also been implemented in a randomized control trial conducted in the Beth Israel Deaconess Center (**Figure 6**).

	Number of Isolates Tested	Ampicillin	Amoxicillin/Clavulanate	Cefoxitin	Aztreonam	Piperacillin/Tazobactam	Cephalothin	Ceftazidime	Ceftriaxone	Cefotaxime	Cefuroxime	Amikacin	Gentamicin	Piperacillin	Ciprofloxacin	Meropenem	Imipenem	Trimethoprim/Sulfamethoxazole	Tetracycline	Nitrofurantoin Only Urines Tested	Percent of isolates from urine
Escherichia coli (IP+ICU)	96	[illegible]	[illegible]	95.12	71.84	92.26	[illegible]	71.84	71.84	72.02	70.41	98.81	82.74	[illegible]	65.81	100	100	63.69	[illegible]	95.95	47.02
Klebsiella pneumoniae (IP+ICU)	42	[illegible]	90	98.57	94.12	95.71	88.24	94.12	94.29	94.29	92.85	100	94.29	[illegible]	85.71	100	100	84.29	85.28	79.17	24.29
Enterobacter cloacae (IP+ICU)	13	[illegible]	[illegible]	[illegible]	65.91	65.91	[illegible]	70	70.45	70.45	[illegible]	100	100	65.91	95.45	100	100	90.91	88.89	--	18.18
Enterobacter aerogenes (IP+ICU)	3	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Serratia marcescens (IP+ICU)	10	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	100	[illegible]	[illegible]	[illegible]	100	94.44	[illegible]	100	100	100	[illegible]	[illegible]	--	0
Citrobacter koseri (IP+ICU)	2	[illegible]	[illegible]	100	100	100	[illegible]	100	100	100	[illegible]	100	100	100	[illegible]	100	100	100	[illegible]	--	50
Citrobacter freundii (IP+ICU)	2	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Proteus mirabilis (IP+ICU)	16	[illegible]	100	100	100	100	87.5	100	100	100	100	100	75	79.17	75	100	[illegible]	62.5	[illegible]	--	11.54
Morganella morganii (IP+ICU)	2	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Providencia stuartii (IP+ICU)	2	[illegible]	[illegible]	100	100	100	[illegible]	100	100	100	100	100	[illegible]	100	100	100	100	100	[illegible]	--	33.33
Escherichia coli (OP)	234	[illegible]	61.8	96.09	83.12	93.59	[illegible]	83.55	83.19	82.83	80.09	100	89.66	[illegible]	77.29	100	100	[illegible]	[illegible]	96.91	84.19
Klebsiella pneumoniae (OP)	69	[illegible]	79.71	91.04	91.3	94.2	73.53	92.54	92.75	92.75	88.24	100	97.1	[illegible]	89.71	100	100	89.86	82.35	[illegible]	73.91
Enterobacter cloacae (OP)	10	[illegible]	[illegible]	[illegible]	87.5	90	[illegible]	100	88.89	80	[illegible]	100	70	[illegible]	90	100	100	70	88.89	[illegible]	50
Enterobacter aerogenes (OP)	8	[illegible]	[illegible]	[illegible]	100	87.5	[illegible]	87.5	87.5	87.5	[illegible]	87.5	100	75	85.71	100	100	75	71.43	[illegible]	50
Serratia marcescens (OP)	6	[illegible]	[illegible]	[illegible]	100	100	[illegible]	100	100	100	[illegible]	100	100	100	100	100	100	100	[illegible]	[illegible]	33.33
Citrobacter koseri (OP)	10	[illegible]	80	70	100	100	[illegible]	100	100	100	[illegible]	100	100	[illegible]	100	100	100	100	90	[illegible]	30
Citrobacter freundii (OP)	4	[illegible]	[illegible]	[illegible]	100	100	[illegible]	100	100	100	[illegible]	100	75	75	100	100	100	75	100	100	25
Proteus mirabilis (OP)	13	69.23	100	91.67	100	100	72.73	100	100	100	92.31	100	76.92	76.92	100	100	[illegible]	100	[illegible]	[illegible]	30.77
Morganella morganii (OP)	5	[illegible]	[illegible]	80	100	100	[illegible]	100	100	100	[illegible]	100	80	100	100	100	100	100	80	[illegible]	20
Providencia stuartii (OP)	1	[illegible]	[illegible]	100	100	100	[illegible]	100	100	100	100	100	[illegible]	100	100	100	100	100	[illegible]	--	0
Shigella (TOTAL)	0	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Salmonella (TOTAL)	54	90.74	98.15	[illegible]	96.04	100	[illegible]	100	100	100	[illegible]	[illegible]	[illegible]	94.23	75.93	100	100	94.44	96.3	--	--

Figure 4. An example of the population-level antibiogram design (Ref: Am J Infect Control. 2010 Nov;38(9): e25-30. doi: 10.1016/j.ajic.2010.02.015. Epub 2010 Jun 8).

Figure 5. An example of the personalized antibiogram design in iAMS

Figure 6. The personalized antibiogram designed by the Beth Israel Deaconess Medical Center (JAMIA. 2021 Sep; 28(9): 1826–1833).

Testing and field testing process

In the testing phase, we checked at least 20 microbiology reports that had at least one of the following antimicrobial-resistant pathogens: carbapenem-resistant (CR)-*Escherichia coli*, *CRKP*, CR-*Morganella morganii*, CR-*Acinetobacter baumannii*,MRSA, vancomycin-resistant (VR)-*Enterococcus faecium*, and VR-*E. faecalis* from the hospitalized patients in CMUH. We looked at each original microbiology report and compare with the visualized antibiogram. We also checked the microbiology reports without any positive culture. In the field-testing process, we check the accuracy of personalized antibiogram periodically and when there are any abnormal results reported by physicians.

Optimizations after usability testing

In the usability testing, we received several suggestions from the physicians and have been optimizing the antibiogram based on these suggestions, including:

(1) Extend the time period to six months: To demonstrate a more comprehensive history of antimicrobial culture history, we extended the time period from prior 3 months to prior 6 months.

(2) Label the important antimicrobial pathogens: To assist the timely identification of patients with high-risk of important antimicrobial resistant pathogens that are under infection control surveillance, we label the pathogen names with orange color. These antimicrobial resistant pathogens include: CR-Enterobacteriales (CRE), CR-*A. baumannii* (CRAB), MRSA, and vancomycin-resistant Enterococci (VRE).

(3) Re-arranging the order of the columns: Originally, the columns of time, culture source, colony count, and bacteria name were on the right of the antibiogram. To make it easier to see the bacteria name, we rearranged the order of the columns to make the columns of time, culture source, colony count, and bacteria name on the left of the antibiogram.

(4) Add MIC value: Sometimes the physician will use the MIC value to determine the antibiotic prescription, especially for the susceptibility results of "intermediate (I)". We will add the MIC value next to the "S", "I", "R" when the physician clicks on the SIR boxes.

Request for personalized antibiogram

The key driver for the antibiogram visualization is the tedious work and tremendous time and efforts to summarize all microbiology reports for the past few months, especially in patients with long infection history. Traditionally, physician needs to go to the exam report to find each of the microbiology exam report, then open each report to read the microbiology report text, as exampled in **Figure 7**. However, using the personalized antibiogram of iAMS, all culture reports in the past 6 months can be automatically summarized in one single figure.

Alerting recommendation

The antibiogram is designed on the basis of population-level antibiogram and also on a webpage. The main purpose of the personalized antibiogram is to summarize the infection history and to highlight the resistant pathogens before the antibiotic prescription. The function of warning for the inappropriate antibiotic order is already implemented in the prescription CDSS section of iAMS

Figure 7. An example of the traditional way to examine a patient's infection history.

Sepsis and mortality risk prediction and monitoring

An AI model for detecting sepsis and predicting mortality was developed, which simultaneously improved the operation efficiency and maintained high accuracy at the same time. The system can also automatically track the AI risks in patients with suspected infection. It records sepsis and mortality risk on a daily basis, and a trend chart was generated. This provides single-point risk and extended long-term trend changes.

MDRO detection/prediction

Through machine learning, mass spectrometer signals are used to predict drug resistance, including MRSA and CRKP, and even key colistin drug resistance can be predicted. The related results and notifications will be sent by short message service (SMS) to physicians.

Matrix-Assisted Laser Desorption/Ionization Time-of-Flight Mass Spectrometry (MALDI-TOF MS) is a rapid and accurate diagnostic technique used for the identification of microorganisms (**Figure 8**), including bacteria and fungi. By incorporating MALDI-TOF MS data into the AI model, it can improve the accuracy of drug resistance prediction by considering the specific pathogens involved in the infection and their potential resistance patterns.

Regarding the use of data elements and MALDI-TOF MS in predicting drug resistance in hospitals in Asia and globally, specific information may vary. Based on available data, it has been reported that 29 clinics in Taiwan have implemented Bruker MALDI-TOF MS systems, while 14 clinics have Biomerieux MALDI-TOF MS systems. These numbers reflect the adoption of this technology and highlight the potential for its use in predicting drug resistance (**Figure 9**).

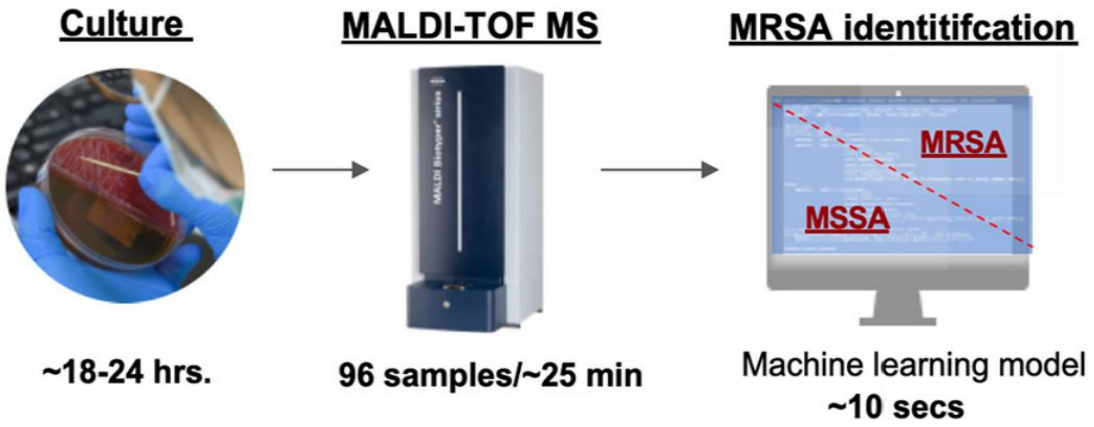


Figure 8. MALDI-TOF MS

Figure 9. Global market 4,401 sites

Intelligent Antibiotic clinical decision support system

Clinical information and infection control data required for infectious diseases are integrated into a clinical decision support system (CDSS). The system can automatically provide appropriate antibiotic and dosage recommendations based on drug sensitivity CLSI guidelines, body weight, and liver and kidney function.

Governance

The iAMS was developed by a team of 40 experts from various departments/centers **(Figure 10)**: Departments of Infectious Diseases, Chest Medicine and Critical Care, Pharmacy, and Information Technology, Centers of Laboratory Medicine, Big Data Center, and Artificial Intelligence (AI). There were 12 PhDs and 14 masters on the team, as well as three professors, four associate professors, and seven assistant professors **(Table 2)**.

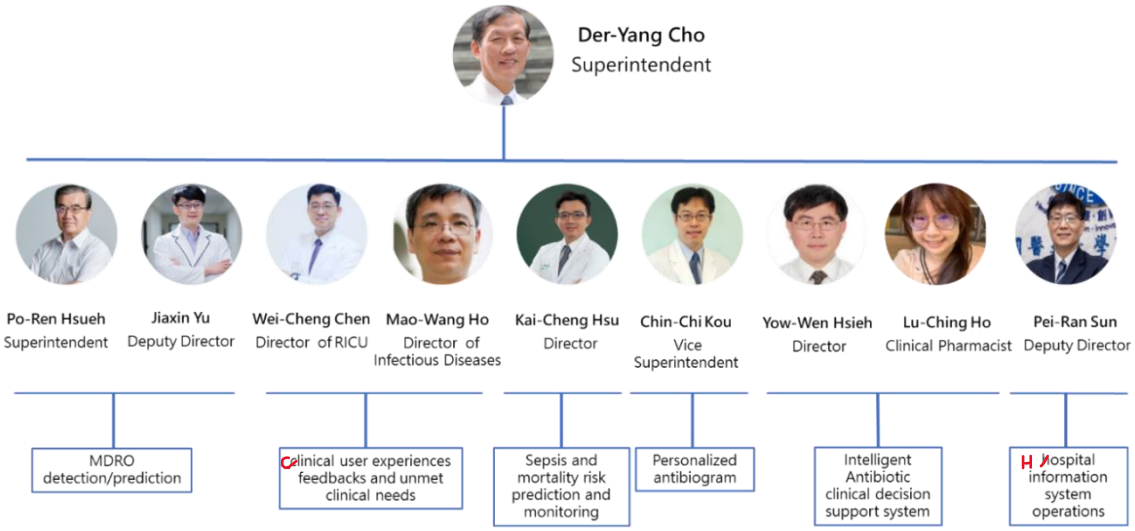


Figure 10. Organization chart of key team members of iAMS

Clinical Transformation enabled through Information and Technology

Personalized antibiogram

The Personalized antibiogram integrates the microbiology reports from the past three months and visualizes the culture results and susceptibility tests **(Figure 11)**. This tool can be easily linked with the structuralized and usually standardized microbiology reports to be implemented in different EMR settings. The antimicrobial susceptibility results are shown in different colors: red represents R (resistant), yellow represents I (Intermediate), and green represents S (susceptible). The Personalized antibiogram also provides culture source information and colony counts (for specific culture sources such as urine and sputum). In addition, the Personalized antibiogram highlighted the four groups of important MDROs, namely CRE, CRAB, MRSA, and VRE. This allows physicians to quickly grasp the patient's infection journey and understand personalized epidemiology, which can help in empirical antibiotic treatment and mitigate the burden of summarizing complex EMR data.

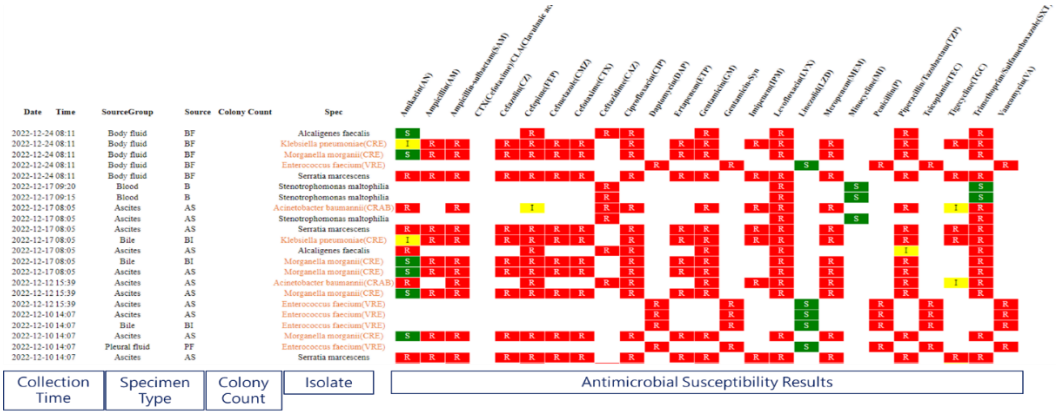


Figure 11. Personalized antibiogram in iAMS

Sepsis and mortality risk prediction and monitoring

To assist in sepsis diagnosis and mortality within 7 days, AI models have been developed using information from over 30 patients, including vital signs and complete blood count (CBC) reports. The AI models use the maximum and minimum values of vital signs and CBC reports within three days. Each feature obtained is normalized to reduce the influence of different range values, and some are then derived into additional features (e.g., shock index: heart rate/SBP). Through the analysis of the SHAP values, a few suitable and important features that could be easily accessed were selected for the final model. To compare various machine learning methods, all models adopt a 5-fold cross-validation method to obtain AUC measurement scores. Moreover, the current general scale used (such as SIRS, qSOFA, SOFA, and MEWS) is also used for verification, and the results show that the XGBoost model performs the best. The system can also automatically track the AI risks in patients with suspected infection. Once the iAMS system was triggered, the sepsis and mortality risk prediction and monitoring system recorded the AI risks on a daily basis, and a trend chart was generated. This can assist in treatment decisions by providing long-term trends with observations of major changes **(Figure 12)**.

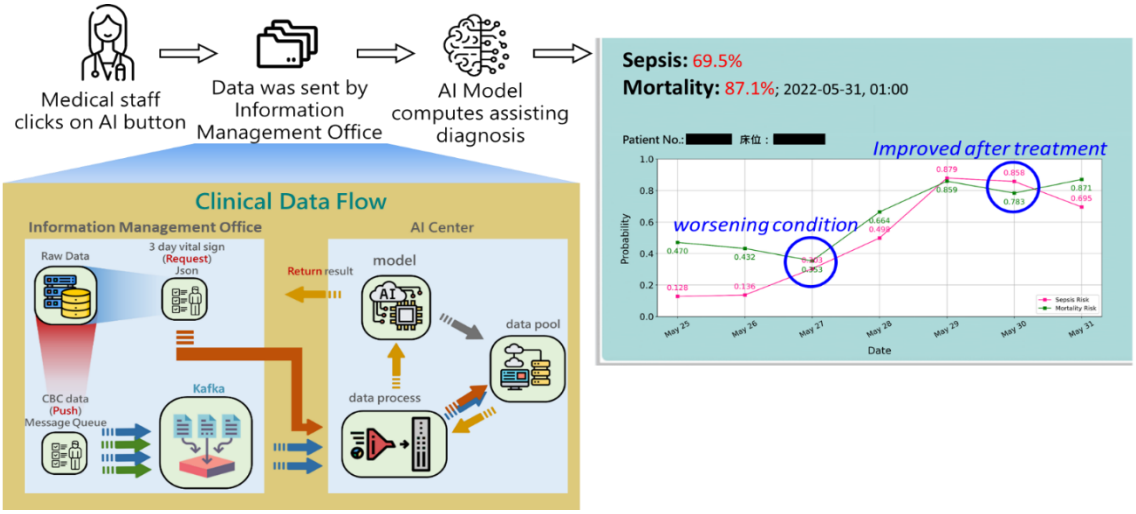


Figure 12. Automatic dataflow of sepsis and mortality risk prediction and monitoring in iAMS

Additionally, the system is now updated with larger font size of risk value in red, and there are three colors painted as the background of the trend chart, which shows the warning level of AI risks (**Figure 13**). If the risk of sepsis or mortality is not zero, the probability will be shown in red to alert clinicians to pay attention to related situations; if the features are not enough for a successful inference, the sign "Not enough data" will be shown on the interface.

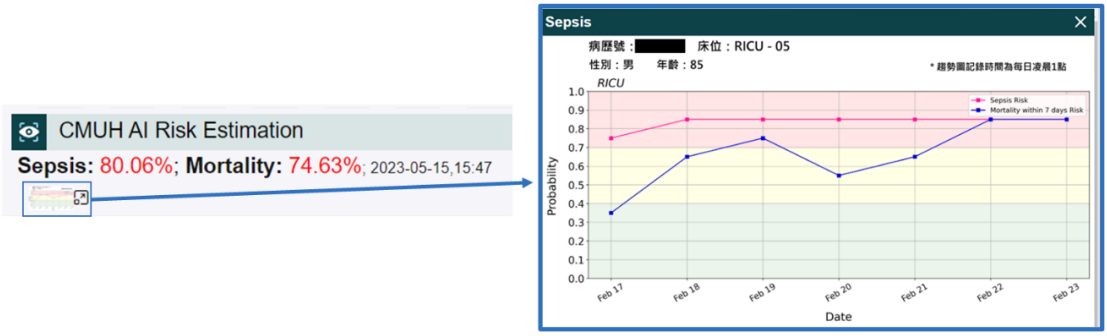


Figure 13. User Interface of sepsis detection and mortality prediction

MDRO detection/prediction

MALDI-TOF MS is a rapid technology for microbial species identification (Lin et al, 2022). MDRO detection/prediction is based on MALDI-TOF MS, which extracts additional information to enable antimicrobial susceptibility detection/prediction. We have trained a light gradient-boosting machine (lightGBM) model that uses machine learning (ML) to predict antimicrobial resistance directly from MALDI-TOF mass spectra profiles of clinical samples. The lightGBM models adopt the 5-fold cross-validation method to obtain AUC measurement scores. Validation against a panel of clinically important pathogens, including MRSA (Yu et al, 2022), CRKP, CRAB, carbapenem-resistant *Pseudomonas aeruginosa* and ceftazidime-resistant *Stenotrophomonas maltophilia* (Yu et al, 2023), has resulted in AUC values from 0.8 to 0.91 and reduced the time by 37 hours compared to traditional workflows, demonstrated the potential of using ML to substantially accelerate antimicrobial resistance determination, and has made a change in clinical management **(Figure 14)**.

The development steps included clinical isolate culture, MALDI-TOF analysis, ML modeling and validation, protein marker identification, and docking simulation. Time spent on sample culture, MALDI-TOF analysis, and MRSA determination using an ML model.

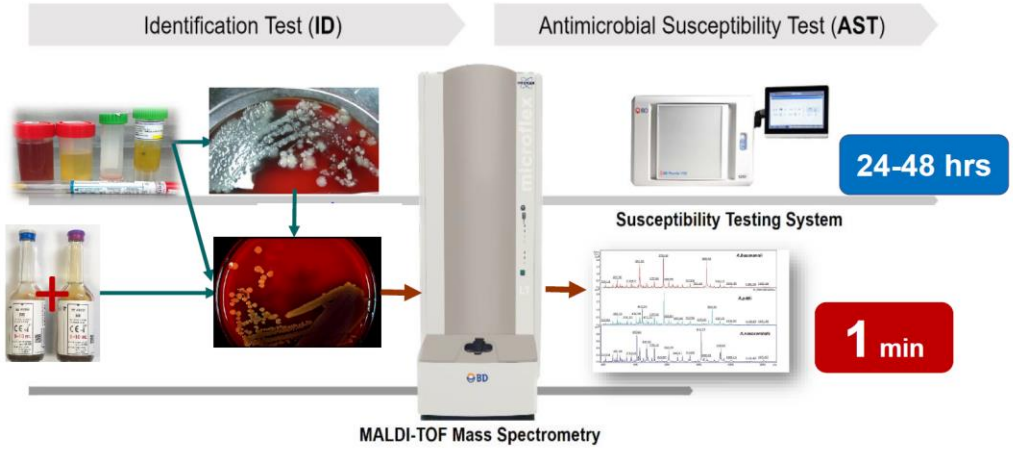


Figure 14. Analytical flowchart of MDRO detection/prediction in iAMS

Intelligent Antibiotic clinical decision support system

The Intelligent Antibiotic clinical decision support system includes the recommendation of drug treatment (considering age, liver and kidney function, and body weight), effective antibiotics for targeted strains, drug costs, warning reminders, and special patient dosing recommendations. Intelligent innovation technology, information technology (IT), and expert rules are used on all de-identified data to provide medical staff with rapid pathogen identification and early diagnosis of unknown and known infections, and the system recommends and helps determine personalized drugs for specific patients. This system was integrated into a hospital's Healthcare Information System (HIS) and has more than 17 functions. A patient's weight, age, and liver and kidney function are taken into consideration to make personalized adjustments to different antibiotics, infusions, flow rates, and doses, which can significantly reduce near-miss events.

The iAMS provided medical history, medications, laboratory results, progress notes, commendations and guidelines for the treatment of infections and reports from specialists

(**Figure 15**). When the physician deviates from the recommended antibiotic choice by iAMS, a notification is displayed on the pharmacist review system (**Figure 16**). The system integrates microbial culture and infection-related prediction results into the Electronic Medical Record (EMR) and automatically sends messages to physicians. In cases where the Intelligent Clinical Decision Support System advises against the physician's decision, the pharmacist will contact the physician and document the discussion (**Figure 17**), ensuring proper adherence to the established workflow.

Figure 15. The recommended antibiotic choice by i.A.MS.

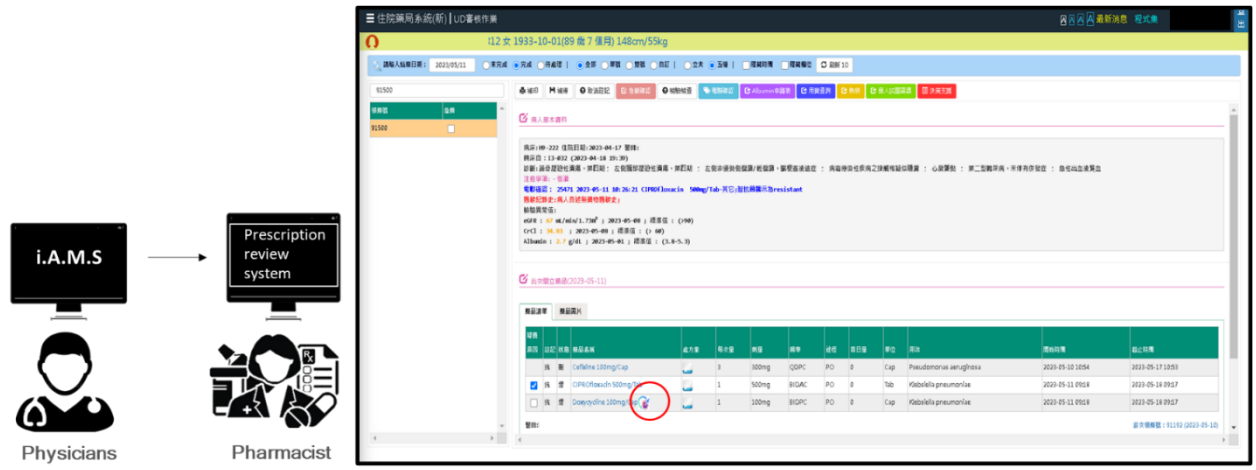


Figure 16. Notification on the pharmacist review system

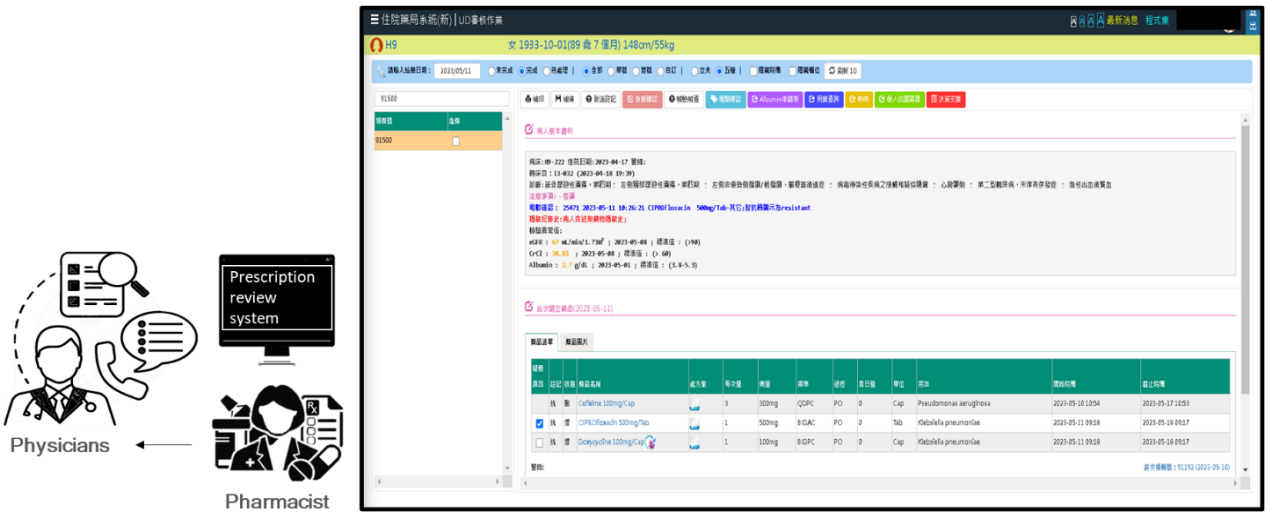


Figure 17. Risk management program

Improving Adherence to the Standard of Care

Additionally, iAMS is now 100% implemented and used in CMUH. The overall times of visits have reached more than 100,000 since its deployment in June 2021 (as of the end of 2022, the cumulative times of visits have reached 146,438) with a monthly average of visits of 11,274 in 2022 **(Figure 18).**

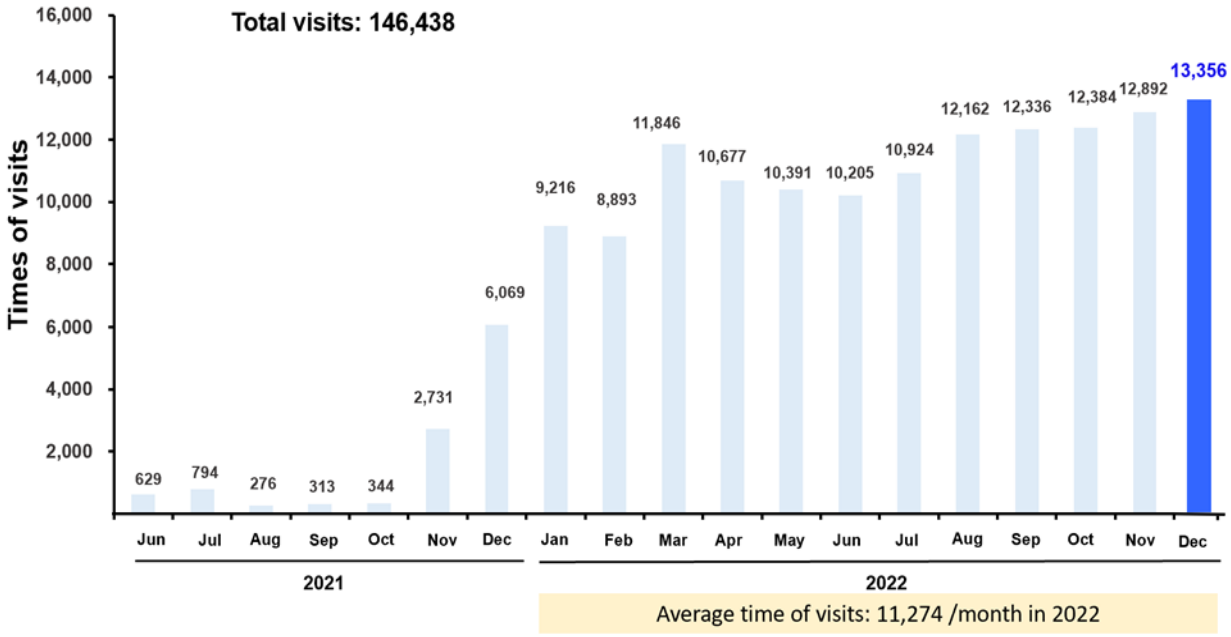


Figure 18. Monthly times of visits of iAMS (as of December 31st, 2022).

"Sepsis Risk and Mortality Prediction" has been used more than 65,000 times since its launch in April 2021. The usage per working day is approximately 300 to 400 times, the non-working day is approximately 150 to 300 times, and the weekly usage can reach approximately 2,000 times. The use of hospitals has gradually become more popular. The accuracy of the models is over 80%. In November 2021, the AI sepsis risk prediction was used for approximately 1,800 patients, and more than 1,400 cases of actual non-sepsis and 70 cases of sepsis were detected, with a correct rate over 80%.

"MDRO detection/prediction" processes over 15,000 protein profiles and protein quality records, as well as the corresponding clinical antibiotic sensitivity test results. In total, 19,788 drug resistance predictions were made. From January to June 2022, 15,000 bacterial resistance risk predictions were successfully provided and showed consistency of about 95% with the microbial culture final report.

To ensure the integrity and confidentiality of hospital information when it is transmitted between the user's computer and the website, regardless of the confidentiality of the content of the system, the CMUH uses the HTTPS protocol for transmission to ensure that users can connect securely. Through the "Transport Layer Security Standard" (TLS) communication protocol, it provides three important information security protection nets: encryption, data

integrity, and verification. CMUH has also passed the ISO 27001 International Information Security certification and ISO/CNS 29100 de-identification certification. The data have completed the de-identification process to ensure that patient information is not leaked.

An iAMS is integrated into the clinical operation process of the hospital in an unknown way, making good use of the active push mechanism to make the entire medical process closely related, forming a fast-response network, achieving real-time and highly efficient medical decisions so that patients can receive early treatment and recover as soon as possible, to improve the quality of the entire medical care. In the satisfaction survey, most users showed positive thoughts about the system.

Improving Patient Outcomes

After the system was launched, the mortality rate due to sepsis was successfully reduced. The survival rate was significantly improved compared to that in the previous year. Taking *S. aureus* as an example, it was found that survival rate increased by about 11.7% after the platform was introduced **(Figure 19A)**, and the improvement in *K. pneumoniae* infections was even more notable (23.7%) **(Figure 19B)**. For approximately 1,600 patients with bacteremia at Emergency Department in CMUH per year, the iAMS helps correct and accurate medication with 555 patients, facilitates a lower inpatient length of 1,110 days, keeps 34 more patients from ICU inpatients, avoids 22 deaths, and reduces approximately 7.33 million New Taiwan Dollar (approximately 0.24 million USD) health insurance costs.

(A) Staphylococcus aureus ***(B) Klebsiella pneumoniae***

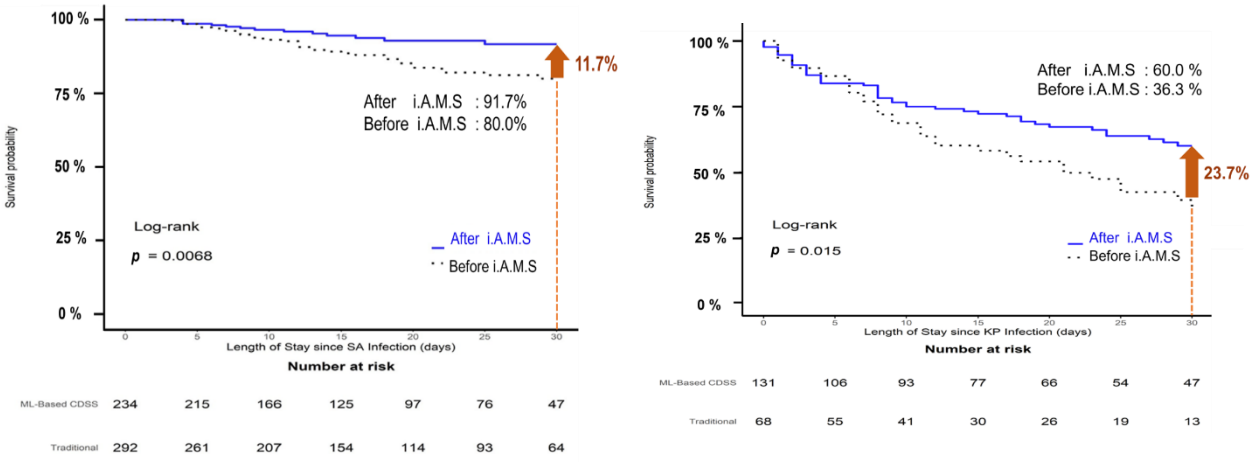


Figure 19. Survival rates at 30 days after hospitalization before and after implementation of iAMS (A) *S. aureus* (B) *K. pneumoniae*.

This retrospective clinical case analysis included 58 cases of CRKP infection. Schematic presentation of time to report with traditional culture and MALDI-TOF MS machine-learning prediction. The median time interval (saving) between the preliminary results and the final report was 1.4 days, with first quartile and third quartiles of 0.9 and 2.9 days, respectively **(Figure 20)**. Physicians can access the drug resistance prediction result 34 h earlier than the traditional culture report, which makes it possible to prescribe correct and appropriate antibiotics as soon as possible to save more patients from delayed diagnosis. In this study, 79.2% (19/24) of the patients with CRKP infection received inappropriate empirical antibiotics, and the antibiotic regimen was changed in 73.7% (14/19) of cases after receiving the preliminary ML prediction results. Furthermore, 38.2% (13/34) of the patients who received preliminary results died at hospital discharge. The mortality rate was high in patients with CRKP infection (10/24, 41.7%) who received inappropriate empirical antibiotics (8/19, 42.1%). In contrast, a lower mortality rate was observed in patients with CRKP infection who underwent antibiotic regimen adjustment after notification of the preliminary results (4/14, 28.6%) (Yu et al, 2023).

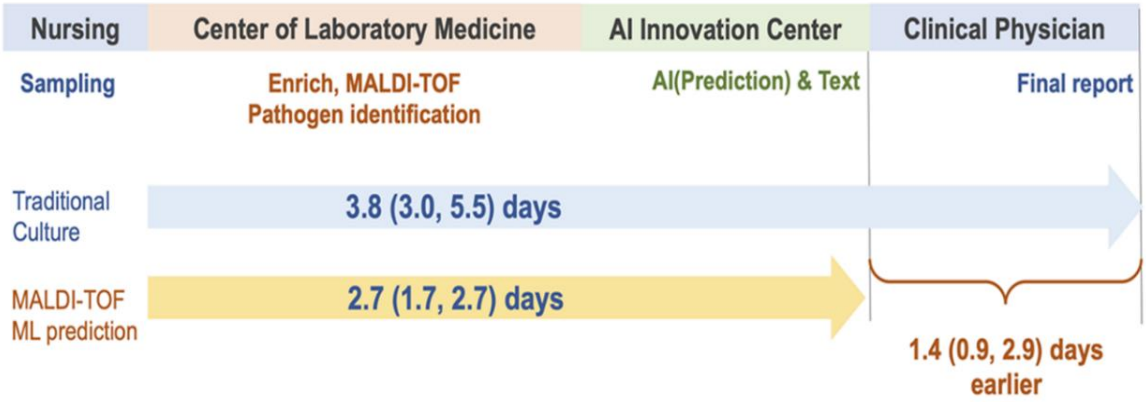


Figure 20. Median time interval between the preliminary results and the final report of carbapenem-resistant Klebsiella pneumoniae.

This system significantly decreased the clinical workload by reducing the time spent on considering antibiotic prescriptions by up to 75%. The monthly near-miss (inappropriate doses, frequencies, or flow rate of intravenous infusion) events were 12.1% in February and 21.2% in October of 2021 and reduced to 0 % in March-December 2022 **(Figure 21)**. The comprehensive platform also showed its value in reducing clinical costs, such as antibiotic costs. Antibiotic costs declined (2.66%-19.66% by month between 2021 and 2022) after the implementation of the iAMS **(Figure22)**.

Leveraging the alert system for sepsis detection (refer to **Figure 13**) and the drug resistance notification system, physicians can make decisions about switching antibiotics more rapidly. The corresponding results are shown in **Table 1** and **Figure 1**. The pie chart (**Figure 23**) illustrates the usage of antibiotics in the prediction of MRSA bacteremia. The chart provides insights into the prescribing behavior of physicians and helps guide interventions to optimize antibiotic usage and combat MRSA infections. It depicts the rationality of medication use based on a comparison before and after the implementation of the iAMS intervention. The survival rate performs better when using appropriate antibiotics (**Figure 24**). Moreover, the 14-day mortality rate decreases using iAMS (**Figure 25**).

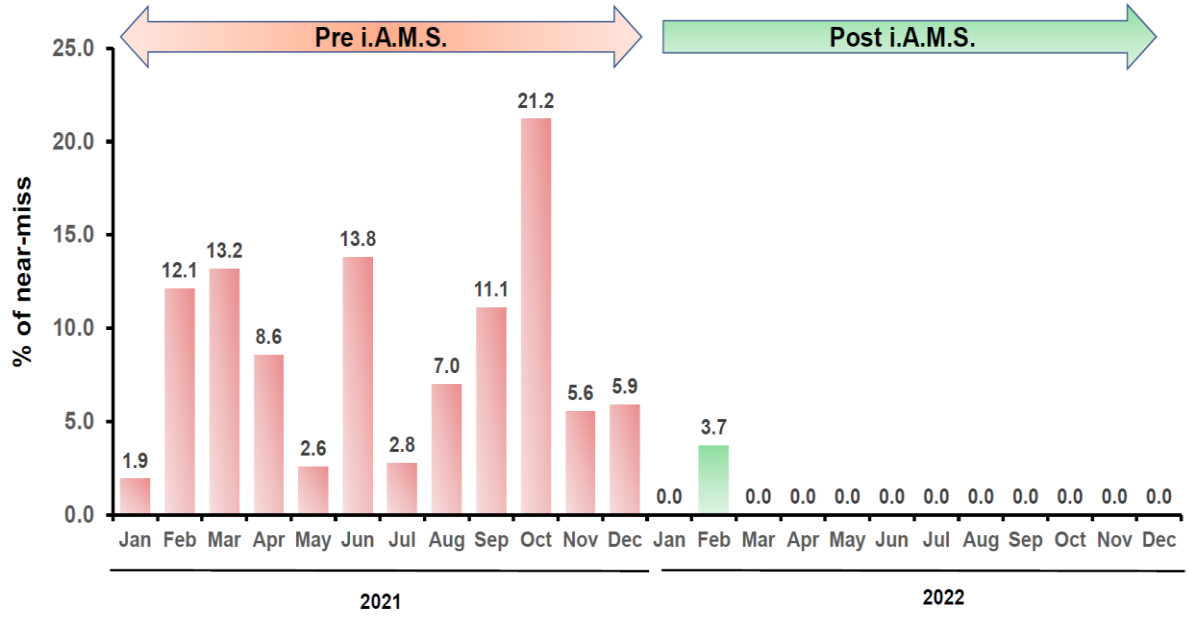


Figure 21. Near-miss rates by month before and after implementation of iAMS, 2021-2022.

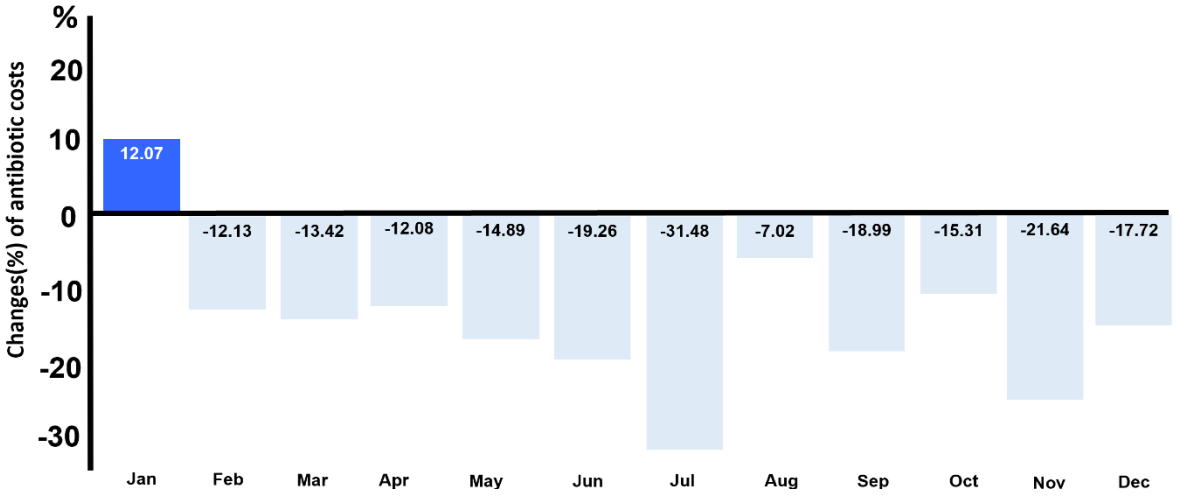


Figure 22. Changes of antibiotic costs by month before and after implementation of iAMS, 2021-2022.

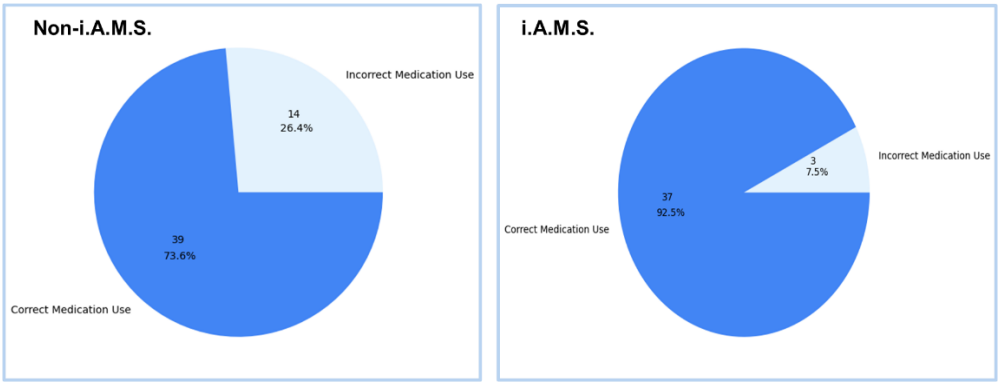


Figure 23. usage of antibiotics in the prediction of MRSA bacteremia

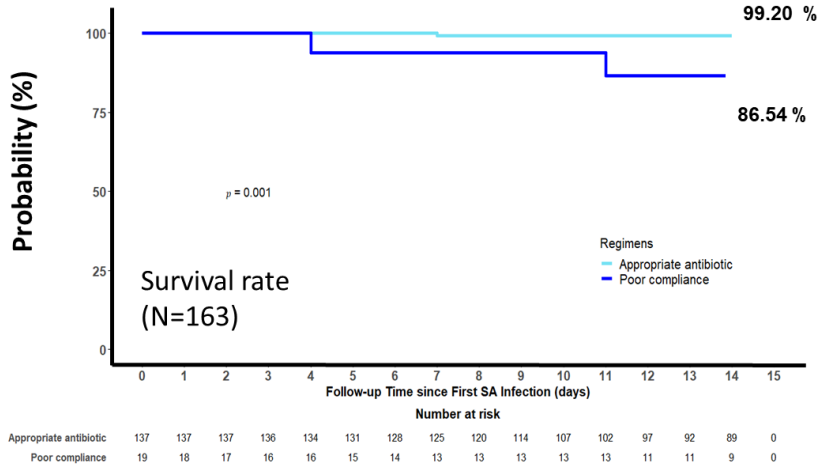


Figure 24. The 14-day survival rate across different specimen types, comparing outcomes before and after the implementation a significant increase of 12.66%.

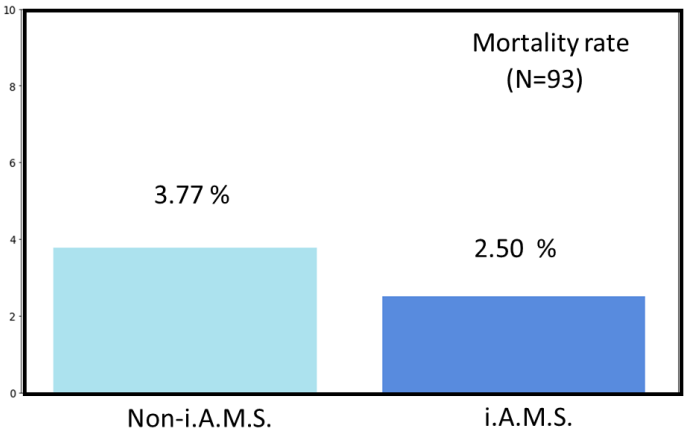


Figure 25. The 14-day mortality rate of patients with MRSA bacteremia, data show indicates a decrease of 1.27% in post-intervention.

Case Study

A 64-year-old male patient who was receiving chemotherapy and radiation therapy for tongue cancer was admitted to the emergency room (ER) because of respiratory failure and septic shock. A Computed Tomography (CT) scan revealed sporadic pneumonia and a psoas abscess **(Figure 26A)**, and empirical antibiotics, such as cefoperazone/sulbactam and levofloxacin, were prescribed.

Blood samples were collected from the patient at 15:40 on December 20th, 2022. Two days later, on December 22nd at 10;43, S. Aureus was identified by MALDI-TOF MS and therefore a MDRO iAMS detection/prediction was done immediately. The result was sent directly as a text message to the patient's attending physician. Based on the prediction, teicoplanin and clindamycin were immediately added to the treatment regimen improving the patient's condition. At 10:28 on December 23rd, approximately 24 h after the AI assisted detection was done, a conventional drug susceptibility testing using the Phoenix automated microbiology system with *S. aureus* revealed MRSA. **(Figure 26B)**.

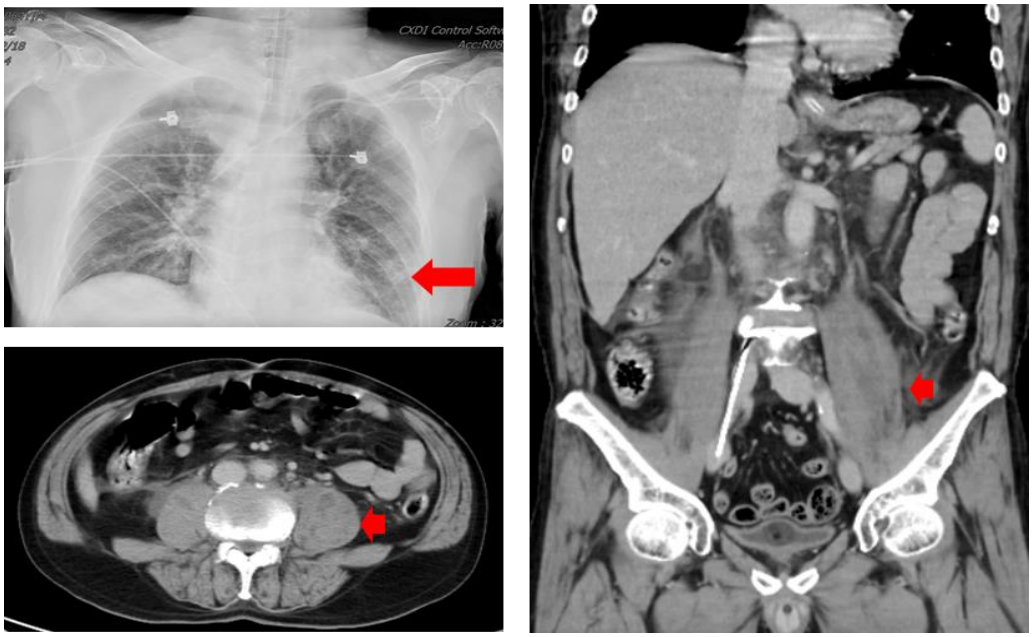
The Intelligent Antibiotic clinical decision support system of the iAMS automatically displayed the appropriate antibiotics automatically for MRSA isolates on the user interface **(Figure 26C)**. Additionally, it provided recommended dosages for each antibiotic based on the patient's specific history of liver and renal function.

Consistent results with MDRO detection/prediction: MRSA was detected on the **personalized antibiogram (Figure 26D)**. The effective use of teicoplanin was further verified after it had been prescribed because of the AI's identification of the drug resistance.

After proper treatment and suitable care, the **sepsis and mortality rate** was significantly improved **(Figure 26E) and a** downward trend in the sepsis and mortality risk was observed, which was also consistent with the changes in the lactate levels.

This patient had the good fortune to receive a medical treatment derived from improved precision and specific, high-quality medication and care because of iAMS, which greatly improved the patient's outcome.

(A)



(B)

Prediction of MRSA: 99%

Thursday 10:43 AM

Wu, [redacted] (male, [redacted])
RICU-[redacted]
Specimen Blood, collected on 20221226, i.A.M.S Oxacillin-resistant S.aureus (MRSA) prediction 99%, for reference only. For any questions about medication, please contact Infectious Diseases.

Wu, [redacted] PatientID: [redacted] Gender: M Birthday: 1958-11-08 Nursing Station: RICU-[redacted] FULL Report

Bacterial Culture Report Specimen: B Attending Doctor: [redacted]

Physician Applied: [redacted] Division: Division of Chest Apply Date: 20221 20 1320 Report Date: 20221223 1028

Report Notes: Execute(Signed) Date: 20221220 1540

Previous Next Inspection Date: 20221220 1435 Inspector: [redacted] Reporter: [redacted]

【Items】

105 Blood Culture*

635 Rapid Minimum Inhibitory Concentration Test for One Strain

【Clinical Symptoms and Initial Diagnosis】

Osteomyelitis

【Reports】

Staphylococcus aureus(MRSA)

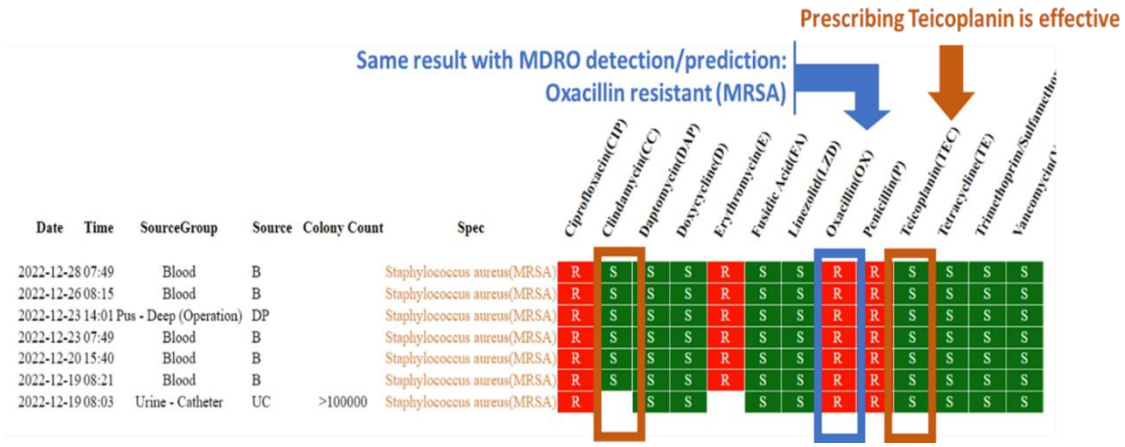
Antimicrobial	MIC (ug/mL)
R :Penicillin(P)	>1
R :Oxacillin(OX)	>4
R :Erythromycin(E)	>4
S :Clindamycin(CC)	<=0.5
S :Vancomycin(Va)	<=1
S :Teicoplanin(TEC)	<=1
S :Linezolid(LZD)	<=1
S :Daptomycin(DAP)	<=1
S :Tetracycline(TE)	<=0.5
S :Doxycycline(D)	<=0.5
S :Trimethoprim/Sulfamethoxazole(SXT)	<=1/19
R :Ciprofloxacin(CIP)	>2
S :Fusidic Acid(FA)	<=1

Gram's stain:Gram Positive Coccus in cluster

(C)


i.A.M.S
加入藥囑
Medication history
Cumulative data
Susceptibility test
MDROs analysis
INF recommendation
Culture(5/11)
【初】 [Deep pus Culture*] 12/29 18:51
B Staphylococcus aureus [增氧]
[Blood Culture*] 12/28 04:42
C Staphylococcus aureus(MRSA) [...
[Blood Culture*] 12/26 08:15
D Staphylococcus aureus(MRSA) [...
[Deep pus Culture (Operation sample)*] 12/23 12:52
Recommended | Cost ↑ Penetration
Pathogen
自選藥品： Pick a drug
Vancomycin(VA)
guidelines antibiogram $304
Vancomycin 500mg/Vial
B C D E
Teicoplanin(TEC)
新增 guidelines antibiogram $516
Teicoplanin 200mg/Vial
B C D E
Doxycycline(D)
antibiogram $3
Doxycycline 100mg/Cap
C D E
On-Call Infectious Disease Doctor :
囑咐訊息
Clindamycin(針劑) 300mg/2mL/Amp

(D)


Prescribing Teicoplanin is effective
Same result with MDRO detection/prediction:
Oxacillin resistant (MRSA)
Ciprofloxacin(CIP)
Clindamycin(CC)
Daptomycin(DAP)
Doxycycline(D)
Erythromycin(E)
Fusidic Acid(FA)
Linezolid(LZD)
Oxacillin(OX)
Penicillin(P)
Teicoplanin(TEC)
Tetracycline(TE)
Trimethoprim-Sulfamethox
Vancomycin(V
Date Time SourceGroup Source Colony Count Spec
2022-12-28 07:49 Blood B Staphylococcus aureus(MRSA) R S S S R S S R R S S S S
2022-12-26 08:15 Blood B Staphylococcus aureus(MRSA) R S S S R S S R R S S S S
2022-12-23 14:01 Pus - Deep (Operation) DP Staphylococcus aureus(MRSA) R S S S R S S R R S S S S
2022-12-23 07:49 Blood B Staphylococcus aureus(MRSA) R S S S R S S R R S S S S
2022-12-20 15:40 Blood B Staphylococcus aureus(MRSA) R S S S R S S R R S S S S
2022-12-19 08:21 Blood B Staphylococcus aureus(MRSA) R S S S R S S R R S S S S
2022-12-19 08:03 Urine - Catheter UC >100000 Staphylococcus aureus(MRSA) R S S S S R R S S S

(E)

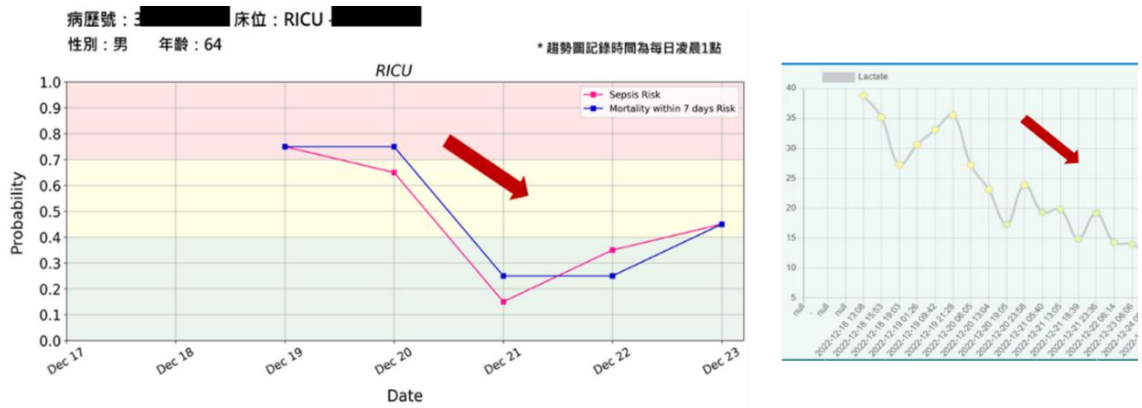

病歷號：[redacted] 床位：RICU [redacted]
性別：男 年齡：64
* 趨勢圖記錄時間為每日凌晨1點
RICU
Sepsis Risk
Mortality within 7 days Risk
Probability
Date
Dec 17
Dec 18
Dec 19
Dec 20
Dec 21
Dec 22
Dec 23
Lactate

Figure 26. Case study. (A) 64-year-old male patient with pneumonia (arrow) and psoas abscess (arrow heads). (B) Automatic text message notification of MDRO detection/prediction results. (C) Recommendations of antibiotics prescription. (D) Resistant patterns of the isolates received previously for the case study patient shown in personalized antibiogram. (E) Trend of sepsis and mortality prediction highly correlated with lactate changes.

Accountability and Driving Resilient Care Redesign

Physicians should click on "iAMS" button to enter the system for prescribing antibiotics, and the data transmission flow will be triggered so that all related data needed will be sent to the back stage. This system was developed to decrease the time of diagnosis of sepsis and save time for early treatment; therefore, all data were sent in real-time to the platform. Each section obtains the required data and shows the results on the user interface after a series of processing steps. **(Figure 27)**

Figure 27. Four platforms of i.A.M.S shown in the dashboard in the hospital information system

Section in red box in **Figure 28** captures the specifics of the prescribed medication, including drug name, dosage, frequency, and doctor's reply record. The purple box in the same figure documents any actions or recommendations made by the pharmacist to address non-compliance, such as counseling the physician, contacting the prescriber, or suggesting alternative treatment options. It also outlines the proposed follow-up actions, including scheduling future appointments or adjusting the treatment plan if necessary.

Figure 28. Non-compliance records

The Internet of Things (Iot) was used to achieve a complete connection and full automation of the instruments to further improve the overall performance. Through the automated connection made among inspection instruments, inspection report results are immediately pushed to the message queue in a unified and standardized structure format. At that point, the AI center can subscribe and access the data at any time. After AI calculations are made, the result is fed back to the message queue. With access to the relevant AI results, the hospital information system will automatically provide physicians with timely clinical decision-making suggestions instead of passively asking the doctor to click on the button to drive the AI calculation. For example, if a prediction of MDRO was provided by the iAMS, a message containing the prediction results would be sent to the attending physicians.

The CDSS is integrated into the entire hospital EMR and provides alerts, recommendations, and warnings to healthcare teams whenever a physician engages with the CDSS to assist with the decision of their antibiotic prescription. The CDSS, as a framework of input-process-output, is designed to improve the availability of important information to the pharmacist and allow them to review the prescription and make the necessary telephone contact and collaboration needed to confirm it with the prescribing physician in a quick and timely manner. **(Figure 29)** Using MRSA and CRKP prediction results as examples, the rates that physicians have responded to the messages were 96 % and 89%, respectively. The accuracy rates of prediction of MRSA and CRKP (in comparison with final results by conventional antimicrobial susceptibility tests) varied with months and were 73% and 84 % in average, respectively. When the final susceptibility results of the isolates are available, physicians will modify or maintain the antibiotic regimens based on the patients' clinical situation, pharmacists' recommendations, and the final susceptibility results of the isolates.

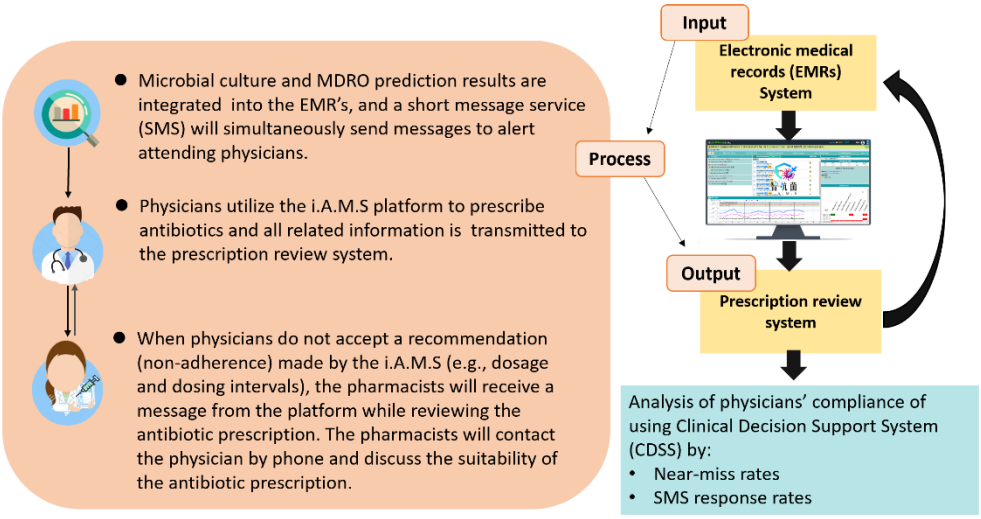


Figure 29. Management Framework for Improving Physician Compliance When Using the Clinical Decision Support System.

Currently, the iAMS is fully integrated into hospital information systems. All antibiotics were prescribed using this platform. Information that was originally scattered in the medical record system, doctor's order system, nursing system, and infection control reports can now be obtained through an integrated platform. Medical records, laboratory data, changes in vital signs, bacterial strain distribution, drug resistance ratio and trend in the unit and whole hospital, microbial culture results and details in the past three months, patient's height, weight, and liver and kidney conditions that are required for prescription of antibiotics functions, are all integrated into the iAMS.

Quality control meetings were held every two weeks by a team of laboratory medicine centers, infectious disease physicians, critical care physicians, laboratory departments, pharmacy departments, information technology centers, AI centers, and big data centers. Comprehensive evaluation and corrections are made for each section regarding data sources and analysis processes of the platform, presentation of the results, and feedback from the clinical use end.

International Exposure

Using AI to fight drug-resistant infections
https://www.healthcareitnews.com/news/asia/using-ai-fight-drug-resistant-infections

Microsoft Asia: Inside Taiwan's 'AI hospital of the future'
https://news.microsoft.com/apac/features/inside-taiwans-ai-hospital-of-the-future

Table

Table 2. The team members of iAMS

Superintendent: Der-Yang Cho

Center/Department	Title	Name
Department of Infectious Diseases	Director	Mao-Wang Ho
	Ward Director	Chih-Yu Chi
	Physician and Specialist	Jia-Hui Chou
Department of Chest Medicine and Critical Care	Director of MICU	Shinn-Jye Liang
	Physician of severe COVID-19 specialty	Yu-Chao Lin
	Director of RICU	Wei-Cheng Chen
	Physician and Specialist	Hao-Yang Zeng
	Physician and Specialist	Jie-Long Chen
Center of Laboratory Medicine	Superintendent and Director	Po-Ren Hsueh
	Deputy Director	Ni Tien
	Technical director	Chiung-Tzu Hsiao
	Supervisor, Session of Microbiology	Hsiu-Hsien Lin
	Staff, Session of Microbiology	Kun-Hao Zeng
	Assistant Professor of Department of Medical Laboratory Science and Biotechnology	Yu-Zi Lin
	Professor of Integrated Medicine Institute	Chao-Rong Chen
	Associate Professor of New Drug Development Institute	Ye Chen
Department of Pharmacy	Director of Pharmacy	Yow-Wen Hsieh
	Division Director of Clinical Pharmacy	Yu-Chieh Chen
	Clinical Pharmacist	Lu-Ching Ho
Department of Information Technology	Deputy Director	Pei-Ran Sun
	Programmer	Ming-Dong Chen
	System Analyst	Chien-Shen Liao
Big Data Center	Vice Superintendent	Chin-Chi Kou
	Associate Researcher	Hsiu-Yin Chiang
	Chief Biostatistician	Che-Chen Lin
	Biostatistician	Zi-Han Lin
	Junior Clinical Data Analyst	Hui-Chao Tsai
	Assistant Algorithm Engineer	Min-Yen Wu
	System Analyst	Chuan-Hu Sun
AI Center	Director	Kai-Cheng Hsu
	Deputy Director	Jiaxin Yu
	Algorithm Engineer	Ya-Lun Wu
	Data Scientist	Ting-An Chang
	R & D Engineer	Bo-Hao Yang
	R & D Engineer	Yun Chen
	R & D Engineer	Chia-Fong Cho
	R & D Engineer	Zhao-Yu Huang
	Research Assistant	Min-Shuan Lu
	Research Assistant	Wen-Feng Lai
	Research Assistant	Sheng-Han Yue