

CONTAINING CROSS-TRANSMISSION OF MULTI-RESISTANT BACTERIA: A PRIORITY FOR CONTROLLING RESISTANCE IN HEALTHCARE CENTRES

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Assistance Publique - Hôpitaux de Paris (APHP), is the largest public healthcare institution in France (38 hospitals, 21,000 beds), and since 1993, it has implemented, step-by-step, a long-term programme for controlling the spread of multi-resistant bacteria, targeting successively methicillin-resistant *Staphylococcus aureus* (MRSA) and then emerging extensively resistant bacteria (carbapenemase-producing enterobacteria (CPE), glycopeptide-resistant enterococci (GRE)). Campaigns promoting the use of alcohol-based hand rub solution for hand hygiene as well as excreta management and antibiotics policy were added to these specific programmes. Local infection control teams in each hospital were supported by a strong commitment of APHP central and local administrations. The prevalence and incidence of MRSA decreased by 75% between 1993 and 2016. Despite an increase in CPE and GRE index cases between 2004 and 2016, mainly due (~70%) to patients with a known history of recent hospitalization or trip abroad, the proportion of these leading to secondary cases decreased from 50 to <10%, due to reinforced procedures. APHP's 20 years of experience shows that the spread by cross-transmission of MRBs such as MRSA, CPE and GRE can be strongly limited in healthcare centres, even at the scale of a large multi-hospital institution.



Increased bacterial resistance is nowadays one of the most important public health issues. Multi-resistant bacteria (MRBs) that spread in healthcare centres and are common causes of hospital-acquired infections, such as methicillin-resistant *Staphylococcus aureus* (MRSA), enterobacteria producing extended-spectrum β -lactamases (ESBL) or carbapenemases (CPE), and glycopeptide-resistant enterococci (GRE) are of particular concern, since antibiotics for treating patients infected by such bacteria are limited, raising a fear of a therapeutic dead end. Controlling the spread of MRBs is therefore a challenge for medical institutions. Overuse of antibiotics, a major factor driving bacterial resistance, usually comes to the forefront of control programmes and sometimes overshadows the other factors favouring resistance. Indeed, cross-transmission, which constitutes the central pillar of communicable diseases due to pathogenic bacteria, such as salmonella, pyogenic streptococci, meningococci, etc., also plays a major role in hospital-acquired

infections caused by opportunistic commensal bacteria (staphylococci, enterobacteria, etc.), particularly in the case of MRBs. Indeed, the complexity of the multiple genomic events that led to MRSA, ESBL or CPE preclude the possibility to engineer “de novo” these MDRs in each new patient case: exchange of chromosomal genes between closely related species (e.g., the genes constituting the different types of SCCmec cassette in MRSA) or imbrication of chromosomal mutations and acquisition of composite mobile elements (plasmids, transposons, integrons, etc.), in which are inserted genes captured from saprophytic bacteria (e.g., for ESBL and CPE). The only way to ensure the success of such genetic “masterpieces” is to transmit them among humans or animals, directly or through intermediate reservoirs, such as the environment. Indeed, Antibiotic pressure plays an important role in maintaining the MRBs in the contaminated hosts. For this reason, all MRBs control guidelines include bundled measures aiming at controlling cross-transmission (e.g., identification

and isolation of carriers, hand hygiene, organization of care) in addition to antibiotic policy.

Assistance Publique – Hôpitaux de Paris, the largest public healthcare institution in France, has implemented from 1993 onwards a long-term programme for MRBs surveillance and control. The objective of the present report is to present the main lines of this programme and share some results obtained during the last twenty years.

Assistance Publique – Hôpitaux de Paris (APHP)

APHP is a public health institution administering 38 teaching hospitals (22 acute care and 16 rehabilitation/long-term care (RLTC) hospitals, spread over Paris, suburbs and surrounding counties), with a total of 21,000 beds (10% of all public hospital beds in France) and serving 12 million of inhabitants. APHP admits approximately one million inpatients per year, employs 22,000 physicians, 20,000 nurses and 30,000 assistant nurses. Administrators and medical committees manage APHP hospitals locally, but decisions on large investments and general medical policy are taken by the central administration. Local infection control teams (LICT) are in charge of prevention and surveillance of healthcare-associated infections in each hospital. Strategic decisions for the whole institution are coordinated by a multidisciplinary central infection control team (CICT: infectious disease physician, bacteriologist, epidemiologist and nurse). The institutional MRBs programme that started in 1993 has progressively included different actions such as promotion of contact precautions, alcohol-based hand rub solutions for hand hygiene, reinforced measures for containing emerging extensively resistant bacteria (CPE and GRE), excreta management policy and campaigns to decrease antibiotics consumption.

The institutional APHP MRBs programme

Each step of the programme was implemented gradually in all APHP hospitals. Actions implemented by all local LICT were supported by a strong commitment of APHP central and local administration.

The first step, in 1993, was to set up bundle measures to control cross-transmission of MRSA whose incidence was at this time higher in France compared to other European countries. The measures called “contact isolation procedures” included identification of MRSA carriers with passive and active surveillance, barrier precautions, training and feedback.

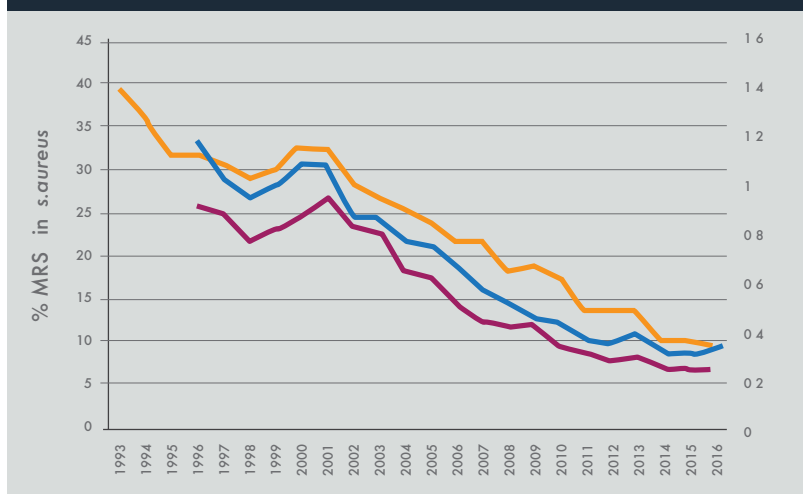
The second step was a large campaign launched in 2001–2002 to promote the use of alcohol-based hand rub solution (ABHRS). This campaign provided pedagogical material to the LICTs; in addition, formal letters from the general director asked all administrators, head of departments and chief nurses to support the campaign.

The third step, in 2006, was to set up a specific strategy for containing emerging extensively resistant bacteria (CPE and GRE), in response to an increase number of cases in APHP hospitals that occurred in 2004/05 though applying the contact isolation procedures as for MRSA. This strategy (“reinforced procedures”) emphasized rapid and stringent application of organizational measures as soon as a first CPE/GRE case was identified: (a) reporting quickly every new case to the APHP central infection control team and alerting the hospital administrator, (b) stopping transfers of cases and contact patients (defined as any patient hospitalized in the same unit during the same period of time as cases) to other units of the hospital or to other hospitals, (c) screening for CPE/GRE contact patients extended to those already transferred from the involved unit to other units at the time of index case identification (screening of contact patients had to be pursued once weekly), (d) reinforce hand hygiene with ABHRS, and cleaning patient cases environments with detergent-disinfectant product; (e) if at least one secondary case is identified, cohorting patients in three distinct areas with dedicated nursing staff: “CPE/GRE patients” section, “contact patients” section and “new patients” section for newly admitted patients with no previous contact with carriers patients, (f) identifying discharged case and contact patients if readmitted. These measure were to be maintained until the outbreak was considered as controlled, i.e., after all CPE/GRE cases have been discharged and after a period of at least three months without new case. To stimulate the efforts made by the LICTs and local administrators, the central infection control team followed the number of new cases, and new outbreaks, and the difficulties in programme implementation and regularly disseminated results within hospitals and central administration. The central infection control team visited regularly the hospitals to help the local teams in applying the programme.

The fourth step, in 2008, was to recommend identification and screening for CPE/GRE of any patient repatriated from foreign hospitals or with recent hospitalization abroad.

Recently, a fifth step has been added in response to a 2012 cross-sectional survey that evaluated the equipment for excreta management and healthcare workers’ practices about excreta elimination in 536 units of APHP hospitals. The survey revealed that the excreta management was mostly a neglected subject, a point that favours cross-transmission of MRBs that are carried in digestive tract (CPE, GRE). The main results were as follows: half of the patients present the day of the survey were wearing diapers or using a bedpan; >1/3 of the toilets were equipped with hand sprayers, a device favouring the spread of faecal material in the environment; half of the bedpans washer-disinfectors were located in room where

Figure 1: Evolution 1993–2016 of the MRSA rates in the hospitals of Assistance Publique - Hôpitaux de Paris: % MRSA in *S. aureus* (orange triangle), MRSA rate per 1,000 days of hospitalisation (blue diamond) and MRSA rate per 100 admissions (purple square)



1,000 hospitalization days (HDs) (Figure 1) (1). The decrease in incidence was more marked in ICU (2.9 to 0.5 / 1,000 HDs) and in surgery (1.5 to 0.4) than in medicine (0.7 to 0.2) and in rehabilitation and long-term care facilities (0.5 to 0.15). Interestingly, we note that the decrease was sharper after the launching of ABHRs campaign in 2001 (see Figure 1).

Increase in alcohol-based hand rub solutions use
 ABHRs are the major tools for enforcing hand hygiene in a hospital setting. Following the campaign's launch in 2001, the consumption of ABHRs progressively increased from 2 ml per hospital days in 1997 up to 44 ml in 2017 in APHP hospitals (Figure 2).

ABHRs were not available; bedpans were usually rinsed before disinfection, mostly in the patient's bathroom; and only a small number of the healthcare workers said they followed an educational programme about excreta elimination. Following this survey, recommendations for the management of excreta have been set up: appropriate outfit, use of disposable excreta collection bag for patient needing a bedpan, removing hand sprayers, regular maintenance of bedpans washer-disinfectors. An educational programme for healthcare workers was also launched. The implementation of some of these recommendations was included as an incentive in evaluation process within APHP institution (quality indicator).

From the antibiotic policy side, a long-lasting campaign was launched in 2006 to decrease, or at least to stabilize, antibiotics consumption and, consequently, the selection pressure on MRBs. This campaign disseminated several messages during a period of 12 years, for example, treat only infection and no colonization, treat only bacterial infections, prevent infections, prevent cross-transmission, re-evaluate antibiotics prescription after 48 hours, and antibiotic treatment to last no longer than seven days.

Impact of the programmes on MRBs rates and hygiene indicators

Decrease in MRSA prevalence and incidence

Between 1993 and 2016, the percentage of MRSA in *S. aureus* decreased in acute care from 39.4% to 9.6% and the incidence rate of MRSA cases decreased from 1.16 to 0.33 per

Control of glycopeptide-resistant enterococci (GRE) outbreaks

The mean number of GRE cases increased by 0.8 cases per month in 2004 and 2005 despite the measures previously used for efficiently controlling cross-transmission of endemic MRSA, but began to decrease when the reinforced procedures (mentioned above) have been implemented, resulting in a decrease by 0.7 cases per month (Figure 3) (2). Moreover, the number of cases per outbreak was significantly lower after implementation of the programme.

Control of carbapenemase-producing enterobacteria (CPE) outbreaks

From 2004 to 2017, the number of index cases of CPE sharply increased from less than 10/year 2009, up to near 400 in 2017 (Figure 4). However, despite this increase, which was

Figure 2: Evolution 1997-2017 of the consumption of alcohol-based hand rub solutions (in ml per hospital days (i.e., patient day) in the hospitals of Assistance Publique - Hôpitaux de Paris (the sudden increase in consumption that occurred in 2009 was due to H1N1 epidemic)

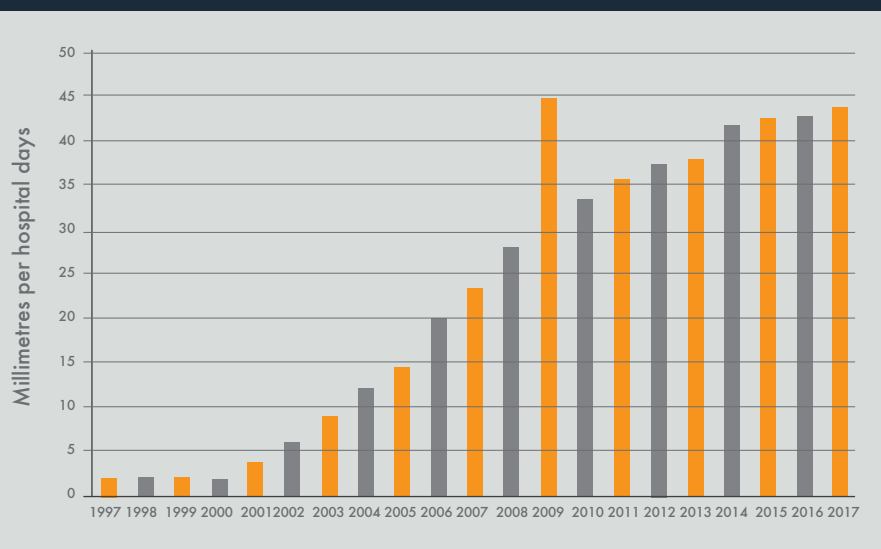


Figure 3: Evolution 2004–10 of the monthly number of glycopeptide-resistant enterococci in the hospitals of Assistance Publique - Hôpitaux de Paris. In 2004–05, classical measures used for controlling MRSA cross-transmission (contact isolation procedures) were applied. Reinforced procedures were implemented in 2006

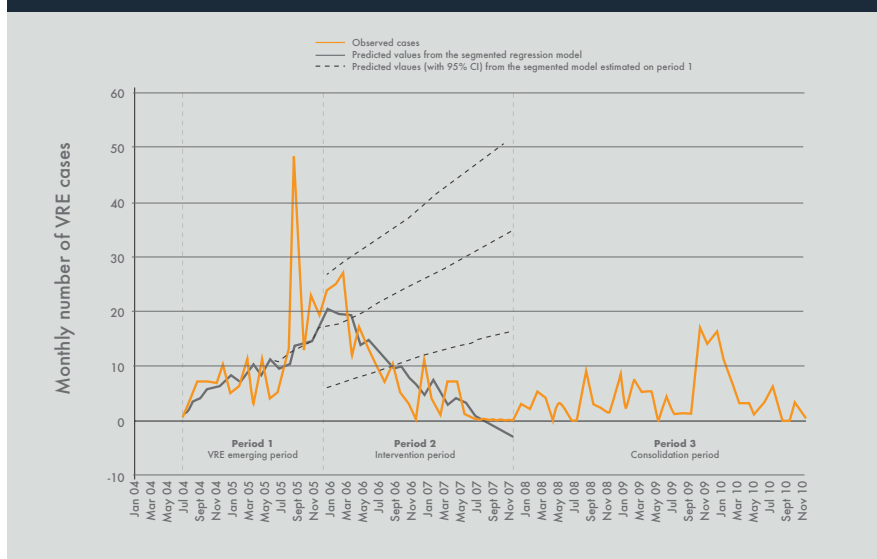


Figure 4: Evolution of the number of CPE index cases (blue columns) and of the proportion of them that led to secondary cases (i.e., outbreaks) (orange line with diamonds), in the hospitals of Assistance Publique - Hôpitaux de Paris, 2004–2017

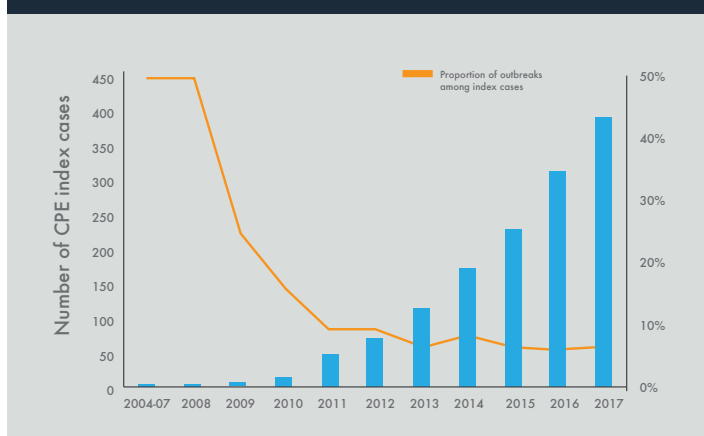
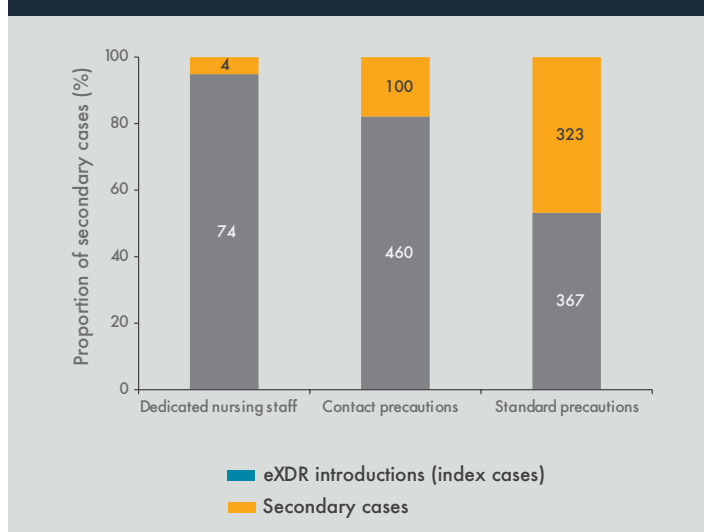


Figure 5: Proportion of secondary cases among CPE cases, according to measures implemented within the first two days around CPE index cases in the 38 hospitals of Assistance Publique - Hôpitaux de Paris, period 2010–2017



mainly due (~70%) to patients with a known history of abroad hospitalization (or stay) within the past year, the proportion of index cases that led to secondary cases (i.e., to an outbreak) decreased from 50% to 8%, as a result of the reinforced procedures introduced in 2006 (see above) (3). Importantly, the types of measures implemented around index cases was clearly crucial and the proportion of secondary cases was lower when dedicated nursing staff were set up, rather than contact precautions (i.e., MRSA procedures) and even far than standard procedure (i.e., hygiene “as usual”) (Figure 5) (5).

Discussion

The institutional programme for controlling MBRs in the 38 hospitals of Assistance Publique - Hôpitaux de Paris progressively included measures targeting successively: (a) MRSA (isolation procedures), MBRs that were considered in 1993 as the priority due to incidence in France markedly higher than in other European countries (EARS-net), and (b) since 2006, reinforced procedures aiming at controlling the spread of emerging extensively resistant bacteria (CPE and GRE). In parallel, specific campaigns have been launched to increase the use of alcohol-based hand rub solutions and decrease antibiotic consumption.

These bundle measures, mainly comparable with those largely described in the literature, succeeded in markedly decreasing MRSA and containing CPE and GRE.

The APHP experience clearly shows that the most aggressive measures (reinforced procedures) are more efficient in controlling CPE/GRE than contact precautions (isolation procedures), which however were sufficient to decrease MRSA spread. Indeed, the rate of CPE/GRE outbreaks was lower when cohorting separately CPE/GRE cases, contact patients and new patients, with dedicated nursing staff for each cohort. Not only occurrence of outbreaks differed according to measures implemented around index cases, but also the size of outbreaks and the number of secondary cases were higher when only isolation procedures or standard precautions were used. We should note that quickly applying isolation procedures around index patients was not always sufficient to avoid secondary CPE/GRE cases, a fact justifying regular screening of contact patients in such situations in order to rapidly detect secondary cases.

In addition, the sharp increase in alcohol-based hand rub solutions use starting in 2001, as well as excreta policy (4), undoubtedly helped to improve the general level of hand hygiene at APHP. Whereas antibiotics consumption was on a continuous raise in the 1990s and beginning of 2000s (up to 570 defined daily doses per 1,000 hospitalization days in 2005), the campaigns on antibiotic policy launched in 2006 stabilized the figures and even led to a slight downward trend (data not shown), a point that at least eased the selective pressure on MRBs.

We have emphasized above that the classical measures successfully used for controlling MRSA cross-transmission (contact isolation procedures) were not effective enough to control CPE/GRE outbreaks. Only the reinforced procedures, implemented in 2006, finally allowed such control. The reasons for this apparently striking fact are actually obvious. CPE/GRE (and ESBLs as well) share several critical features concerning their dissemination potential: (a) they are hosts of the digestive tract and consequently are easily disseminated by fecal route (or urines in case of urinary infection) whereas MRSAs are hosts of nasopharynx, a more remote site, (b) their resistant traits are harboured on mobile element, increasing the risk of bacteria to bacteria dissemination whereas methicillin resistance is chromosomal, (c) the bacterial loads are far higher for CPE/GRE (108/gr of feces, i.e. $\sim 10^{10}$ excreted per day by a carrier) than for MRSA (maximum $\sim 10^8$ bacteria in nose). It is a good example of the need to adapt infection control policy to the characteristics of the targeted organism.

We should raise the point that limitations in nursing staff may be an obstacle to dedicating healthcare workers to a single index CPE/GRE case. In this situation, control measures could be adapted, e.g., by organizing “moving forward cases” beginning with MRB-free patients and ending with cases patients. In all settings, it is of foremost importance to promote the use of alcohol-based hand rub solutions, which are the most efficient and convenient tools for hand hygiene in hospital settings. Consumption of ABHRs represents an easy to obtain and self-speaking indicator of hygiene quality that is nowadays used at European level. Management of excreta (stools and urines) is another point of major importance to control the spread of faecal bacteria in hospitals. Healthcare workers should be asked to be especially vigilant about hand hygiene during excreta management and encouraged to use disposable excreta collection bags for the CPE/GRE carriers requiring the use of a bedpan.

In conclusion, the long-lasting experience (more than 20 years) in the APHP hospitals shows that the spread by cross-transmission of MRBs, such as MRSA, CPE and GRE, can be strongly limited in healthcare centres by specific control programmes, even at the scale of a large multi-hospital

institution, providing that all stakeholders, infection control teams, medical and nursing staff, microbiologists and hospital administrators, are convinced, stimulated and involved (6, 7). Controlling other types of MRBs that have already spread worldwide in hospitals, and also in the community, animal setting and environment, such as ESBLs, would require far more ambitious and multifaceted programmes that should include increased hygiene in the general population (sanitation in schools and other closed communities, family hygiene, etc.), strong environmental policies (e.g., processes in sewage treatment plants, clean water supply, food control), as well as organization of farming and husbandry in order to cut the intricate chains of transmission. If we fail in setting up such programmes, the antibiotics that are efficient to treat ESBL infections (carbapenems) will be overused and will favour in response the emergence of CPEs, the ultimate step of multi-resistance in Gram negative bacilli. ■

Professor Vincent Jarlier, MD (1977 Paris), Post-doctoral fellow H. Nikaido's lab., UC Berkeley USA (1988-89), PhD (1990 Paris). Dr Jarlier was the bacteriologist coordinator of multiresistant bacteria survey in French hospitals; founder of the French national observatory for antibiotic resistance survey (ONERBA), and is Director of the French National Reference Centre for mycobacteria and resistance to antituberculous agents. He is a member of the French national antibiotic programme committee, the steering committee of the European Antimicrobial Resistance Survey system (Ears-net, ECDC), and of the advisory board of the European Committee on Infection Control (EUCIC). His areas of research (296 references in Pubmed) are: antibiotic resistance, nosocomial infections, control of multiresistant bacteria outbreaks in hospitals and tuberculosis.

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