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REVIEW

Conflicts of interest in infection prevention and control research: no smoke without fire. A narrative review

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Abstract

Conflicts of interest (COIs) do occur in healthcare research, yet their impact on research in the field of infection prevention and control (IPC) is unknown. We conducted a narrative review aiming to identify examples of COIs in IPC research. In addition to well-known instances, we conducted PubMed and Google searches to identify and report case studies of COIs in IPC and antimicrobial resistance (AMR), which were chosen arbitrarily following consensus meetings, to illustrate different types of COIs. We also searched the Retraction Watch database and blog to systematically identify retracted IPC and/or infectious disease-related papers. Our review highlights COIs in academic research linked to ties between industry and physicians, journal editors, peer-reviewed journals' choice for publication, and guideline committees participants and authors. It explores how COIs can affect research and could be managed. We also present several selected case studies that involve (1) the chlorhexidine industry and how it has used marketing trials and key opinion leaders to promote off-label use of its products; (2) the copper industry and how reporting of its trials in IPC have furthered their agenda; (3) the influence of a company developing "closed infusion systems" for catheters and how this affects networks in low- and middle-income countries and guideline development; (4) potential perverse incentives hospitals may have in reporting healthcare-associated infection or AMR rates and how government intervention may restrict AMR research for fear of bad publicity and subsequent negative economic consequences. Finally, the analysis of reasons for the retraction of previously published papers highlights the fact that misconduct in research may have other motivations than financial gain, the most visible form of COIs. COIs occur in the field of research in general, and IPC and AMR are no exceptions. Their effects pervade all aspects of the research and publication processes. We believe that, in addition to improvements in management strategies of COIs, increased public funding should be available to decrease researchers' dependency on industry ties. Further research is needed on COIs and their management.

Keywords: Conflicts of interest, Integrity, Industry sponsorship, Public-private partnerships, Infection prevention and control, Antimicrobial resistance, Retraction

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Introduction

One definition of a conflict of interest (COI) is: "a set of circumstances that creates a risk that professional judgement or actions regarding a primary interest will be unduly influenced by a secondary interest" [1]. It is important to note that while COIs may exist, they do not inevitably lead to misconduct. Also, it has been suggested that industry sponsorship does not inevitably lead to bias either, but is rather a risk factor for bias, which could include, for example, selective reporting of favourable outcomes [2]. COIs can be both financial and non-financial; the main focus of our review will be on the former.

Non-financial conflicts of interest are frequently overlooked for various reasons, but perhaps because they are "more difficult to detect, measure, and evaluate" [3]. They can be broadly divided into academic, professional, and personal interests. Some authors believe that there should be no conceptual distinction between financial and non-financial COIs, even though they require different management strategies [3]. In a "publish or perish" academic environment, researchers are under pressure to have their studies' results shown in the best possible light. A non-financial COI could lie in the apparent bias that editorial board members of journals seem to publish significantly more in their own journals than do editors of other journals [4]. Another example could lie in attribution of grants, where rivalry or cronyism may compete with objective evaluation of research projects [5].

It is important to point out that public-private partnerships may result in beneficial outcomes for the "greater good" in the health sector and have increased in number and scope in recent years, with the creation of entities such as the Global Alliance for Vaccines and Immunization (GAVI) and the Global Fund [6]. For example, these partnerships have resulted in improved access to antiretroviral therapy for people living with HIV, increased immunisation of children, and eradication of polio [6].

The aim of this narrative review is to evaluate the extent of the influence of COIs on research and the process of publishing in the field of IPC and AMR, particularly in the context of critical care. We first provide an overview of how COIs can affect academic research in general and then describe some self-explanatory case studies in our field.

Methods

In addition to well-known instances of COIs, we conducted non-systematic exploratory PubMed and Google searches using the key words: "conflict of interest", "ethics", "publication bias", "non-financial conflicts of interest", "infection control", and "critical care". We also reviewed "Related citations" and reference lists of retrieved publications. After several consensus meetings, a group of co-authors selected case studies illustrating how COIs can affect research and the process of publication in IPC and AMR, based on prior knowledge or after a literature search. These case studies were chosen arbitrarily and are not intended to represent an exhaustive or systematic compilation of all COI events in IPC/AMR, but rather to serve as salient and sometimes well-known examples. The choice of the themes was determined by those that we deemed most relevant to critical care, i.e. decontamination of ICU patients using chlorhexidine, copper surfaces, central line-associated bloodstream infections, and AMR.

Take-home message

Conflicts of interest (COIs) exist in all fields, and pervade all aspects of research, including in infection prevention and control. We need large-scale improvements in the management strategies of COIs as well as increased public funding to allow researchers to decrease their dependence on industry ties.

Because the analysis performed by Tringale et al. [7] did not analyse Infectious Diseases (ID) and Critical Care physicians separately, we accessed the Open Payments database (openpaymentsdata.cms.gov) and extracted the per-physician value of general payments for these specialties for the year 2015. We report the total number of physician recipients as well as the median, maximum, and mean value of payments. The number of physicians receiving > $10,000 is also presented.

We also searched the "Retraction Watch" blog (www.retractionwatch.com) on 19 April 2018 using the search terms "Infectious diseases" and "Infection control" and the Retraction Watch Retraction Database (www.retractiondatabase.org) on 9 May 2018 in the subject category "Medicine—Infectious Diseases". Retraction Watch is an organisation affiliated with the non-profit Center for Scientific Integrity and holds, to our knowledge, the only database compiling retracted scientific peer-reviewed papers. Among other activities, it reports information about retracted publications through a blog and feeds a database on papers subjected to retraction, correction, and issues of concern, among others. We excluded papers unrelated to ID, related to general ID only, including papers primarily dealing with HIV, hepatitis, or tuberculosis, vaccine development/immunity studies, and community outbreaks unrelated to healthcare.

Conflicts of interest in academic research

Industry-physician ties are frequent, as shown by the US Open Payments, a national transparency program that collects and publishes information about financial relationships between the healthcare industry (i.e.

pharmaceutical and medical device manufacturers) and providers (i.e. physicians and teaching hospitals) [8]. Analysis of this database showed that industry has provided payment to approximately 48% of all US-based physicians in 2015, for an estimated total of $2.4 billion USD [7]. We analysed the Open Payments database and extracted data on general payments for ID and Critical Care physicians (Table 1).

Editorial COIs are also important: an analysis of the Open Payments database showed that approximately half of the editors of a selection of high-impact journals received a general payment from industry in 2014 [mean $28,136 (standard deviation $415,045); median $11 (interquartile range $0–2,923)], with some receiving over $1 million [9]. Furthermore, COI policies were accessible on the websites in only a third of these journals [9]. Even in the absence of editorial COIs, journals themselves, as well as or through their parent societies or publishers, have potential COIs. It has been previously shown that for high-impact general medical journals, industry-supported randomised trials not only help in increasing revenue via the sale of reprints (e.g. 11 million sold by *Lancet* in 2005–2006), but also increase impact factors because of more frequent citation [10]. There is no unified approach from the part of journals on how authors should declare COIs; we have made available COI policies from a selection of intensive care and IPC and/or ID journals (Supplementary Table 1). Many biomedical journals ($n=4,052$ on 24 May 2018) adhere to the International Committee of Medical Journal Editors recommendations [11], and although they set "ethical and editorial standards for article publication", they are not infallible, and it is unclear to what extent adherent journals interpret and/or follow the recommendations [12]. The recent change in policy by the *New England Journal of Medicine* to loosen policies on COIs was harshly criticised by *BMJ* editors [13].

Although physicians who are guideline committee members, or guideline authors, should also disclose COIs, this disclosure is either incomplete at best (e.g. 89% of disclosures in World Health Organization (WHO) guidelines [14]), or scant (11% in the US National Guideline Clearinghouse [15]). Yet, disclosure of COIs is only feasible if organisations have policies or mechanisms in place to require or facilitate them; however, it appears that over a third lack them entirely [16]. Nearly all professional societies receive financial support from industry and have industry-sponsored events during their scientific meetings. They should "strictly adhere to standards for commercial support", as was commented on an Association of Professionals in Infection Control and Epidemiology educational event sponsored by a company producing rapid tests for MRSA, and, at the same time, had sessions where the speakers were either employees of the company or advocates of extensive surveillance strategies [17].

There is large potential for COIs at academic institutions; a US-wide survey in 2006 performed in all medical schools showed that two-thirds of departments and 60% of department chairs have a financial relationship with industry [18]. These relationships were deemed positive by the majority of department chairs for provision of continuing medical education; however, most respondents stated that there was no effect on the financial security of their department, increased institutional funding, or recruitment of new faculty [18]. The authors of the study ask: "If the majority of [institutional academic-industry relationships] have no effect on these important functions of departments, then why do they exist?" [18], raising the possibility that chairs are reticent to acknowledge influence. It was stated almost 20 years ago that "the business goals of industry influence the mission of the medical schools in multiple ways" when unclear boundaries between industry and universities exist [19]. Therefore, management of institutional COIs is as important as individual COIs, and its principles follows the same lines [20]. Unfortunately,

Table 1 Per-physician value of general payments; Open Payments database, USA 2015

	No. of physician recipients (%)	General payments			No. (%) of physicians receiving > $10,000
		Median value (IQR), US $	Maximum value, US $	Mean value (SD), US $	
Internal medicine[a]	103,588 (51.1)	248 (73–959)	4,536,302	N/A	5167 (5.0)
Orthopaedic surgery[a]	20,300 (67.9)	420 (117–2041)	38,392,184	N/A	2232 (11.0)
Infectious diseases[b]	4,975 (N/A[c])	191 (57–859)	809,340	5,126 (26064)	436 (8.8)
Critical Care[b]	5,152 (N/A[c])	103 (30–269)	5,018,080	2,360 (70,493)	143 (2.8)

IQR interquartile range, *N/A* not applicable, *SD* standard deviation

[a] Data from Tringale et al. JAMA 2017

[b] Data calculated from the OpenPayments website

[c] Denominator unknown

many institutions lack policies to manage COIs, as demonstrated by studies in France and the US [21, 22].

This may also have an effect on medical education, as physicians-to-be "become accustomed to receiving gifts and favors from an industry that uses these courtesies to influence their continuing education" [19]. It has been previously demonstrated that exposure to pharmaceutical marketing during medical education increases prescription of these drugs after graduation [23], and, conversely, restricting or regulating interactions between, or gifts from, pharmaceutical sales representatives in academic medical centres reduces prescription of detailed drugs [24–26]. This makes it a matter of serious concern to know that, in certain settings, up to 90% of medical students have had direct interaction with pharmaceutical drug representatives [27–30].

How do COIs affect research?

When analysing published research, it appears that almost a quarter of investigators are affiliated with industry and that industry sponsorship is associated with threefold higher odds of pro-industry conclusions [31]. Could this be due to selective publication policies? An analysis of US-based studies registered in the clinicaltrials.gov database showed that despite federal regulations (Sect. 801 of the Food and Drug Administration Amendments Act) requiring submission of results of clinical trials within 12 months of completion, 30% of studies did not achieve public disclosure of results in the 4-year period following completion [32]. Also, 29% of large ($\geq$ 500 participants) RCTs registered in clinicaltrials.gov were unpublished [33]. The reasons for non-dissemination of studies are diverse, and, because the dissemination process involves a large number of stakeholders, it may be unclear at which level the obstacle lies [34]. What is clear is that a company's policy to require submission for publication of all research, irrespective of the findings, may mitigate publication bias [35, 36]. It appears however that industry-sponsored studies report favourable results 30% more often than non-industry sponsored studies [37]. Concrete examples in IPC/AMR are given below.

Furthermore, a phenomenon known as "spin"—where the interpretation of published study findings is hyperbolic (or contradicts) regarding the actual results—seems to be associated with industry sponsorship [38]. This is not without consequences: physicians reading abstracts of RCTs that contain spin are more likely to rate effects of the intervention as being beneficial [39], and spin in abstracts was associated with a fivefold higher prevalence of spin in press releases or media coverage of RCTs [40]—a potentially dangerous amplification as results head to the public sphere. On the latter, presence of COIs in social media are undoubtedly understudied, but they seem to exist and are not necessarily disclosed, for example when physicians tweet about products or companies with whom they have an undisclosed financial relationship [41, 42].

Ethical considerations of COIs

Editors of some journals have spoken out and called for submitting authors to "play fair" [43]. But there is also an ethical imperative to "publication and dissemination of the results of research", and researchers should not forget that they "are accountable for the completeness and accuracy of their reports", as stated by the Declaration of Helsinki [44].

Management of conflicts of interest

Some experts believe that disclosure alone may not be an effective strategy to manage COIs [45] or may even exacerbate the problem of bias [13]. Previously, a framework for management of COIs has been proposed that "provides a unified strategy to evaluate conflicts of interest in academic research" [46]. Briefly, the elements providing justification to accept a COI were (1) the presence of a shared primary interest; (2) freedom from constraints (i.e. "an exit strategy"); (3) assessment of applicability; (4) disclosure to allow independent review [46].

WHO takes COIs seriously and has described how to identify and manage COIs for its guideline development [47]. The Declaration of Interests form at WHO describes COI as "any interest declared by an expert that may affect or reasonably be perceived to affect the expert's objectivity and independence in providing advice to WHO" and must be collected and reviewed before experts can be accepted as part of the guideline development group (GDG). In principle, those who have major COIs, whether financial or non-financial, cannot be appointed to the GDG. For WHO guidelines, the primary interest is "to serve WHO's Member States by producing recommendations that improve the health and well-being of populations". WHO acknowledges that all involved in developing a guideline have secondary interests, and COI arises when the primary and the secondary interests are not aligned. WHO decides the level of participation of each individual to the GDG meeting, depending on the extent of COI. A similar approach is taken when WHO organises other types of technical meetings with external experts. In 2017, WHO, jointly with major funders and international non-governmental organisations, made a statement to improve public disclosure of results from clinical trials [48]. WHO manages International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/), a global database of clinical trials from 17 registries around the world, whose goal is to enhance transparency

of clinical trials through timely registration and public disclosure of results. The improved public disclosure of results will allow for more informed decisions, particularly "negative" clinical trials where COI is often involved [37].

Conflicts of interest in infection prevention and control research: case studies

Chlorhexidine

A 2016 Reuters investigation explored the extent of the COIs in the field of IPC [49]. Sage Products funded a study in 2006 showing that chlorhexidine gluconate (CHG) wipes were more effective than soap and water baths in preventing vancomycin-resistant enterococci (VRE) colonisation, decreasing the incidence of VRE acquisition from 26 to 9 colonisations per 1000 patient-days [50]. The family foundation of the co-founder of Sage, also chairman of the board, donated $1 million for research to the institute of the senior author of this study [49]. Over the following few years, Sage funded six further trials that support bathing patients with chlorhexidine wipes [51–55]. A subsequent NIH-sponsored cluster-RCT did not find chlorhexidine wipes to be effective in reducing healthcare-associated infections (HAI) in five adult ICUs [56]. Yet, a number of systematic reviews and meta-analyses have concluded that the use of CHG wipes is effective [57, 58]. The antiseptic market is huge. According to BCC Research, the CHG market is projected to grow by $2.3 billion between 2015 and 2020 [59]. The Reuters article cites a 2014 CDC survey reporting that 63% of US hospitals routinely bathed their patients with CHG, although it is unclear (due to the phrasing of the question in the survey) which patient population this applies to or the frequency of bathing [60]. Interestingly, the US Food and Drug Administration (FDA) approved the wipes solely for preoperative skin preparation [49].

Sage's CHG wipes underwent a total of four recalls up to 2016 because of contamination with *Burkholderia cepacia*, and the company received a warning letter from the FDA on "significant violations of current good manufacturing practice regulations" regarding inadequate microbiological screening methods [61]. The 2008 recall occurred during one of the studies, causing it to be suspended, and although this was mentioned in the publication [52], the fact that six patients in the trial were infected by *B. cepacia* was not mentioned [49]. Another effect of this dramatic increase in use has been a growing concern about overuse of chlorhexidine, in terms of both bacterial resistance and the increases in severe allergies and other adverse events in patients [62, 63].

A recent scandal erupted in the US involving industry-physician ties and alleged endorsement of a company's product in an organisation's recommendations, constituting clear COI. The National Quality Forum (NQF) is a "not-for-profit, nonpartisan, membership-based organization" whose aim is to "catalyze improvements in healthcare" [64]. At the time the alleged events occurred, Dr. Charles Denham was co-chair of the Safe Practices Committee of the NQF, but also editor of the *Journal of Patient Safety*, and chairman of the Texas Medical Institute of Technology (TMIT), a non-profit medical research organisation centred on patient safety [65]. The US Department of Justice brought legal charges against CareFusion over allegations "that it violated the False Claims Act by paying kickbacks and promoting its products for uses that were not approved" by the FDA [66]. Indeed, Dr. Charles Denham received $11.6 million from CareFusion, under the contention that "the purpose of those payments was to induce Denham to recommend, promote and arrange for the purchase of ChloraPrep® by healthcare providers" and that "Denham solicited and received these payments in exchange for influencing the recommendations of the NQF and for recommending, promoting and/or arranging for the purchase of CareFusion's product, ChloraPrep®, in violation of the Federal Anti-Kickback Statute" [67]. After Denham paid $1 million and CareFusion paid $40.1 million, the lawsuit was settled, and "The claims resolved by the settlement are allegations only; there has been no determination of liability" [66]. After replacing Denham, the *Journal of Patient Safety* wrote an editorial that analysed which of his papers during his tenure as editor presented COIs: nine out of ten of the papers did. The discussion presented in that article is particularly pertinent: "when a COI exists, or the perception of such a conflict, it could, although it does not always, affect the validity of a recommendation" [65]. It goes on to say that COIs undermine the trust of the public and can inhibit the adoption of important measures.

The NQF removed the recommendation to use CareFusion's product from the final 2010 report after an ad hoc review, severed ties with Denham in 2010, and immediately terminated a grant from Denham's foundation (TMIT). It updated its policy to automatically refuse grant agreements when the funder is on the endorsement committee, reviewed previously published reports to make sure Denham's COIs had not changed the content, and updated its COI policy [65].

To underscore the magnitude of the effects that industry may have, it is interesting to note that in its statement on the settlement concerning CareFusion and Denham, the Department of Justice writes that it has reclaimed $15.2 billion recovered in cases involving fraud against federal healthcare programs since 2009 through the False Claims Act [67].

Copper industry

For many years, the copper industry has been seeking novel applications in healthcare, particularly in surfaces, but also pens, linens, and stethoscopes, with several clinical trials being registered in clinicaltrials.gov [68].

One of these industry-sponsored trials suggests that "Copper surfaces reduce the rate of HAIs in the intensive care unit" [69]. However, this study is fraught with irregularities, notably in terms of selective reporting of outcomes (including non-reporting of two pre-specified primary outcomes), but also interpretation of the results. When re-analysed properly, it was found that for the primary outcome of HAIs, there was no significant difference between patients in rooms with copper versus those in rooms without [70]. Furthermore, it was pointed out that there was a lack of biological plausibility, because only 10% of the surfaces in "copper rooms" were copper alloy surfaces and that this would unlikely be the cause of a purported 50% reduction in the neo-primary outcome of "HAI and/or MRSA or VRE colonization" [70]. It remains regrettable that two ulterior industry-sponsored trials cite the results of this study at face value and do not take into account the serious issues that had been raised [71, 72]; this contrasts with an independent evaluation of the quality of the study, which was rated as "very low" to "low", in a recent systematic review, but for high risk of bias (sequence generation and allocation concealment); unfortunately, the selective outcome reporting was not mentioned [73]. The authors of the study contested the quality assessment and defended their study [74].

Another industry-sponsored trial, this time unblinded and nonrandomised, in paediatric ICUs also claimed that introduction of copper-surfaced items was associated with a 19% reduction in relative risk of HAI; the title of the published manuscript begins with "Potential effectiveness of copper surfaces […]" [72]. That the results were not statistically significant was stated in the abstract, but only after the authors claimed that the intervention "resulted in decreased HAI rates". Furthermore, the authors excluded 47.7% of the included patients because of a hospital length of stay of < 72 h "to avoid counting possible infections present prior to admission", whereas this exclusion criterion was not pre-specified in the clinicaltrials.gov record, making it a post hoc exclusion [72].

A recently published multicentre study in a healthcare network with only one author [75] evaluated the effect of copper linens on the rate of HAI in a network of hospitals in the US. It is fraught with a substandard design, statistical analysis plan, and several irregularities in the reporting, among which was the absence of disclosure of the relationship between the healthcare network and the company producing the copper linens [76].

Although there certainly are data that show that copper surfaces reduce the "bioburden" of these surfaces, the clinical translation of these findings in terms of patient outcomes has not been demonstrated, and many practical uncertainties remain [68].

Catheters

The International Nosocomial Infection Control Consortium (INICC) was established in 2002 with the aim of establishing HAI surveillance and prevention in critical care in low- and middle-income countries (LMIC). The network has constantly grown over the past years, and today, 1998 investigators are reporting data from 460 hospitals in 423 cities of 69 countries in Africa, Latin America, the Eastern Mediterranean, Europe, South-East Asia, and Western Pacific [77, 78]. The example of COI given here devalues neither the excellent initiative provided by INICC nor the support given by one of its sponsors, Baxter. It does, however, highlight concerns of publishing (and influencing recommendations in guidelines) low-quality data with the aim to promote a sponsor's product. Four studies, performed in Argentina, Brazil, Italy, and Mexico, concluded that "closed infusion systems" were effective for the prevention of central line-associated bloodstream infections [79–82]. All but one study [79] were non-controlled before-and-after studies with short baseline and intervention periods. The findings of the four studies were further summarised in a meta-analysis, confirming the positive findings of the individual studies [83]. The rationale was to eliminate a potential route of infection due to contamination by ambient air through external ventilation of glass bottles or semi-rigid plastic containers. The validity of these studies is of concern because "closed systems" were introduced to replace glass bottles, but the concomitant surveillance strategy and promotion of multimodal prevention measures were not mentioned. All studies analysed the effectiveness of "closed systems" as though this were the only intervention, ignoring the potential confounding effect of the other measures.

The effectiveness of a technical device should be studied in an RCT because the effect of secular trends can otherwise not be excluded. A later study applied a multistate analysis on data from INICC centres of two cities [84]. While this model is more robust and provides a more conservative estimate, it still modelled the "closed system" as the only intervention.

The study design favoured the studies' sponsor's product, and no study by authors outside of INICC replicated the findings. Shifting to a "closed system" may indeed have its benefits, but no conclusion can be made on its contribution to prevention of central line-associated bloodstream infection. The head of INICC actively

promoted the use of this system in its partner INICC hospitals and influenced guidelines to recommend its use [85, 86], which is of concern given the uncertain evidence.

Antimicrobial resistance (AMR) and healthcare-associated infections (HAIs)

Aside from the numerous COIs surrounding research on novel antibiotic agents and treatment of AMR infections that stem from direct industry financial interest in commodities, other conflicts from within health services or authorities have an impact on how research projects on the control of AMR are chosen, funded, whether or not the results are published. Such COIs are of real concern given that our ability to prevent and control AMR infections depends entirely on our ability to accurately identify where and when such infections occur, to aggregate such information, and to share it in order to compare and ultimately explore appropriate policy options.

Hospitals in competitive environments are often concerned about bad publicity. This is particularly true when it comes to reporting of large outbreaks or hyperendemic rates of AMR infections [87]. Statistics surrounding HAI rates may be particularly sensitive given that they are a very tangible metric with which the public can compare hospitals. Indeed, the COI is strong: reporting high HAI rates may demonstrate poor performance; this is true of even just seemingly high rates in the eye of the layperson who misunderstands these data [88]. This is presumably one of the key reasons explaining that while good surveillance network examples exist, in many countries there are insufficient data to understand the true frequency of HAIs, aggregate and compare data, or initiate the IPC/AMR research necessary to conclusively tackle the problem [89]. Indeed, data from many places in LMIC are missing entirely [90]. There is, however, no compelling evidence that mandatory reporting of HAIs linked to punitive financial measures, such as withholding of reimbursement, has led to voluntary underreporting or "gaming", as is the case in the US Centers for Medicare and Medicaid Services, where reported HAI rates have not decreased as a consequence of this policy [91].

COIs associated with identifying and reporting HAIs also affect governments. Many different surveillance networks currently exist, each for a different geographic area, pathogen, and/or resistance pattern [92–94]. Even where surveillance objectives are similar, the lack of standardisation in definitions and methods limits comparability and research efforts. This raises the question of whether the lack of viable national surveillance in some middle- and high-income countries and the continuing lack of standardisation across networks derives at least in part from the reluctance to make such figures public and comparable. Where resources are more limited, the lack of data and limited standardisation is explainable. However, even in countries where some national surveillance data are routinely collected, governments are not always willing to share it. Indeed, the GLASS initiative, a global WHO-led network set up to collect data on drug-resistant infections, continuously faces the uphill battle of convincing governments to share results to allow for appropriate aggregation and response [95].

As AMR increases, so does the concern of governments, presumably due to concerns related to loss of tourism, including medical tourism, and other image-dependent industries. There are a few well-known cases of governments reacting very strongly when externally publicised infection-related data have put economic interests at risk. The story of the New Delhi metallo-beta-lactamase 1 (NDM-1), a potent carbapenemase, illustrates these concerns. Scandal erupted in 2010 following an article in *Lancet Infectious Diseases* that sounded the alarm that the prevalence of NDM-1 in South Asia has become a worrying public health threat and that medical tourists may become vectors to import those superbugs to the UK [96]. Although by then the enzyme had been identified in several countries including India, Pakistan, and the UK and was later reported in many more [97–99], the direct association of the superbug to India (where it was first identified by Yong in 2009 [100] and further emphasised by Walsh in 2011 [101]) caused outrage—leading some to feel that the authors had unfairly "singled out and made India as the focal point of global interest on antibiotic resistance" [102]. Indeed, the publicity surrounding the case of NDM-1 led to much anger and ultimately an apology from Richard Horton for having unnecessarily stigmatised the city of New Delhi and India [103]. An unintended consequence of this controversy was that the Indian government imposed restrictions on international collaborative efforts on NDM-1 research—e.g. legal obstacles for exporting NDM-1 strains for research purposes outside India. The private health sector in India, accounting for 80% of the country's health expenditure, is attractive for medical tourists, and its worth was approximately $300 million in 2011 [104, 105]. The case of NDM-1 brings to the fore the perceived dangers of being associated with infection and how this can lead to government reluctance to fund, instigate, or even collaborate with research that explores the emergence or transmission of such infections, especially if there is any possibility that they may be singled out. Such inherent COIs require particular attention in our efforts to conduct IPC/AMR research and shape coherent policy moving forward.

Retraction of infectious diseases/infection control publications

There were 265 hits in the database search. We included papers on IPC in the hospital setting and/or AMR related to HAIs/nosocomial microorganisms ($n=22$). We excluded papers unrelated to ID ($n=23$) or related to general ID only, including papers primarily dealing with HIV, hepatitis or tuberculosis ($n=201$), vaccine development/immunity studies ($n=13$), and outbreaks unrelated to healthcare ($n=6$). Table 2 is a summary of the main reasons why a publication was retracted, corrected, or subjected to an issue of concern by the journal mentioned in the database. Supplementary Table 2 reports the papers in more detail; it also includes results found through the blog search ($n=12$) that were not retrieved in the database using the search criteria applied.

The reasons for retraction or correction can be classified into two broad categories. In one, the authors spotted involuntary errors in the results when conducting additional analyses and reported them to the journals for correction or retraction, which is laudable. However, most of the time, few or none in the scientific community had identified those errors. Some retractions are due to errors from the publishers when they duplicate publications. The great majority of retractions fall into the second group and are related to a continuum of other less clear and benign reasons. Disagreements on authorship and the right to use the data between authors, double submissions, violation of the study protocols, voluntary errors in data collection, plagiarism, and major unreported COIs are some of the reasons for retraction found in this sample of IPC/AMR papers.

Table 2 Summary of the main reasons for retraction, correction, or publication of an expression of concern by the journal mentioned in the Retraction Watch database

Number of papers	Main reasons stated in the Retraction Watch database
8	Issues about data, methods, analysis, or results
2	Issues about authorship and data
8	Fabrication of data and/or plagiarism
3	Forged authorship
2	Duplication of article by journal/publisher
2	Duplication of article or submission by author
2	No information available

In this table, only the 27 papers found in the Retraction Watch database are mentioned

Concluding remarks

COIs occur in the field of research in general, with IPC and AMR being no exceptions. They can pervade all aspects of research and the publication process, and their effects are heterogeneous. In many instances, COIs are linked to research facilitation, publication, and knowledge dissemination; in some cases, however, they may be a barrier to the truth. Although the case studies we present are conspicuous examples of COIs, there is little research being conducted in COIs in IPC/AMR. We propose a tentative research agenda (Table 3).

Interestingly, financial COIs were only one of several reasons for retraction/correction of papers identified in the RetractionWatch database, perhaps reflecting "lower barriers of publication of flawed articles" [106]. This highlights that misconduct in research may have other motivations than financial gain, which may be the most visible form of COI. As previously mentioned, non-financial COIs are a major and probably underconsidered driver of misconduct.

Some experts have called for management of financial COIs that goes beyond the traditional practice of

Table 3 Conflicts of interest in infection prevention and antimicrobial resistance control; proposed research agenda

Attempt to quantify prevalence of COI in IPC and AMR
Analyse data from Europe regarding COIs in general, but also in IPC, AMR, and critical care
Investigate whether COIs or industry sponsorship are associated with more favourable outcomes in IPC
Investigate whether IPC and ID guidelines report COIs accurately
Explore how COIs can be reported in a more standardised and transparent manner across all publications
Assess whether the reported absence of COIs by authors/experts in the field of IPC reflects reality by making ad hoc samples in specific domains (e.g. trials on use of devices/supplies tested for preventive effect)
Investigate whether non-publication of selected negative results trials is associated with COIs
Investigate whether type of funding is related with retraction
Investigate non-financial COIs that influence misconduct in research
Evaluate other forms of preventing misconduct in research (e.g. modifying the "publish or perish" paradigm)
Develop software tools to tackle inappropriate or misleading downstream messaging deriving from academic research
Evaluate whether risk of bias assessment tools should include a criterion for industry funding/sponsorship

AMR antimicrobial resistance, *COI* conflict of interest, *ID* infectious diseases, *IPC* infection prevention and control

disclosing them only [13]. We have proposed one such strategy to manage financial COIs [46], but others exist, and it is unclear at this point whether some are superior. Management of non-financial conflicts of interest is not only challenging [107], but has also raised controversy [108]. Alternative incentives, beyond the "publish or perish" environment for researchers may also be required—some journals, in response to what they call "impact factor mania" [109], have discontinued display of the impact factor on their websites [110], although it is unclear whether this will be effective.

One limitation of our review is the fact that most studies on financial COIs stem from the US because of the greater availability of data, including from sources such as the OpenPayments database. Countries in the EU have recently adopted requirements for disclosure of physician payments from industry, under the aegis of the European Federation of Pharmaceutical Industries and Associations (EFPIA); hopefully, some analysis of these data will be undertaken. Indeed, these data are sorely needed in order to build a comprehensive picture of the extent of COIs in areas outside North America.

We believe that along with increased transparency and improved management of COIs, increased public funding is essential for researchers to extricate themselves from potentially problematic relationships. Alternative forms of public funding, i.e. apart from tax-based government funding, could be sought, such as crowdfunding or philanthropy-based funding.

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Compliance with ethical standards

Conflicts of interest
Mohamed Abbas and Stephan Harbarth have worked on an investigator-initiated research project mandated by SwissNoso that was funded by Pfizer USA. SH has received funding by the European Commission and the Swiss National Science Foundation for several clinical studies and has consulted for Sandoz, Bayer, and DNA Electronics. Didier Pittet has received funding from the European Commission and Swiss National Science Foundation for several research and clinical studies. Didier Pittet also works with the World Health Organization (WHO) in the context of the WHO initiative Private Organizations for Patient Safety (POPS) Hand Hygiene. The aim of this WHO initiative is to harness industry strengths to align and improve implementation of WHO recommendations for hand hygiene in healthcare in different parts of the world, including in least developed countries. In this instance companies/industry with a focus on hand hygiene and infection control related advancement have the specific aim of improving access to affordable hand hygiene products as well as through education and research. Walter Zingg has received funding by the European Commission, the European Centre for Disease Prevention and Control, and the Swiss Federal Office of Public Health for research and has consulted for Baxter, Schülke & Mayr, and Carefusion. All other authors have no conflicts of interest to declare.

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