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Dynamics of scientific publications on the MERS-CoV outbreaks in Saudi Arabia

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\section*{A B S T R A C T}

Middle East Respiratory Syndrome Coronavirus (MERS-CoV) is an emerging disease with a relatively high case fatality rate. Most cases have been reported from Saudi Arabia, and the disease epidemic potential is considered to be limited. However, human–human transmission has occurred, usually in the context of healthcare facility-associated outbreaks. The scientific and medical community depends on timely publication of epidemiological information on emerging diseases during outbreaks to appropriately target public health responses. In this review, we considered the academic response to four MERS CoV outbreaks that occurred in Al-Hasa in 2013, Jeddah in 2014 and Riyadh in 2014 and 2015. We analysed 68 relevant epidemiology articles. For articles for which submission dates were available, six articles were submitted during the course of an outbreak. One article was published within a month of the Al-Hasa outbreak, and one each was accepted during the Jeddah and Riyadh outbreaks. MERS-CoV epidemiology articles were cited more frequently than articles on other subjects in the same journal issues. Thus, most epidemiology articles on MERS-CoV were published with no preferential advantage over other articles. Collaboration of the research community and the scientific publishing industry is needed to facilitate timely publication of emerging infectious diseases.

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Introduction

Emerging infectious diseases are a growing cause of major concern worldwide in terms of public health [1]. The importance of immediate collection of reliable epidemiological information, appropriate analysis, and rapid dissemination to relevant stakeholders during an outbreak, is well-recognised in terms of the public health response and containment of the outbreak [2,3]. Information on the causative agent, likely routes of transmission and prediction of how the outbreak might spread, diagnostic criteria, and possible treatments are all relevant. Such information allows public health experts in both national and international agencies and in research settings to formulate and implement prevention policies and strategies based on updated evidence. Dissemination of public health information can be achieved by a number of methods such as online, specialised peer reviewed papers or, for example, on the World Health Organization (WHO) website [4]. However, the primary method for communicating research findings is through the medium of journal articles [5].

One example of a recent emerging infectious disease is the Middle East Respiratory Syndrome Coronavirus (MERS-CoV), a betacoronavirus, which can cause acute respiratory illness in humans, with clinical presentation ranging from asymptomatic to death [6,7]. It was first observed in a 60-year old man with acute pneumonia and subsequent renal failure, who died in a hospital in Jeddah, Saudi Arabia in 2012 [8]. The first human cluster of eleven cases was confirmed retrospectively in a public hospital in Jordan in April 2012 [9]. To date, WHO has been notified of 1800 laboratory-confirmed cases from 27 countries, and of 640 deaths [10]. Most outbreaks have occurred in the Arabian Peninsula, in particular in Saudi Arabia, with occasional spread to other countries, including an outbreak in Korea in 2015 [6]. There have been numerous outbreaks in Saudi Arabia, for example 25 cases in Al-Hasa between April 1st and May 23rd 2013 [11], 255 patients in Jeddah between January 1st and May 16th, 2014 [12,13], 45 patients between March 29th and May 21st, 2014 in King Fahad Medical City in Riyadh, Prince Sultan Military Medical City, between March and April 2014 [14,15], and 130 MERS cases at King Abulaziz Medical City in Riyadh in June–August 2015 [16].

Comparison of queries of the online clinical decision support resource UpToDate with reports of cases was recently shown to be helpful in detection and monitoring of outbreaks of MERS-CoV in Saudi Arabia [17]. Another study examining data related to MERS on the internet-based participatory surveillance system HealthMap suggested that such resources can be helpful in outbreak monitoring [18].

In this review, we analysed the academic publications to four outbreaks that occurred in Saudi Arabia: Al-Hasa 2013, Jeddah 2014 and Riyadh 2014 and 2015. A similar analysis of two outbreaks of severe acute respiratory syndrome (SARS) showed that most articles were published after the outbreaks had ended, even though they had direct public health relevance during the outbreaks [5]. Our analysis included the epidemiology categories and research domains in which journal articles on the four MERS-CoV outbreaks were published; the methodological characteristics of studies in terms of type, design, case definition, and setting; the timeline of publication of studies in relation to the time of the outbreak; and the scientific impact of MER-CoV articles, in terms of level of citations compared to simultaneously published control articles.

Materials and methods

Literature review

We searched the MEDLINE database for all published articles on epidemiology of the MERS-CoV outbreaks in Al-Hasa in 2013 [11], Jeddah in 2014 [12,13], and Riyadh in 2014 [14,15] and 2015 [16]. We searched for all journal articles written in English in which the main subject studied was one of the above MERS-CoV outbreaks. The searches focused on journal articles published during each outbreak to the present. Outbreak dates were taken based on the WHO and the Saudi Ministry of Health (MOH). These dates were (1) April 1st and May 23rd 2013 for the Al-Hasa outbreak, (2) January 1st and May 16th, 2014 for the Jeddah outbreak, (3) March 29th and May 21st, 2014 for the Riyadh 2014 outbreak and (4) June–September 28th 2015 for the Riyadh 2015 outbreak [11–13,16]. The literature search was carried out in September 2016. Separate searches were carried out for each outbreak. The following search equation was initially used for the Al-Hasa outbreak to maximise retrieval of potentially relevant articles and to exclude publication types other than journal research articles:

Search strategy: [Middle East Respiratory Syndrome coronavirus OR MERS-CoV] AND All fields: [Al-Hasa OR Al-Ahsa] AND Publication type: [Journal article] AND Language: [English] AND Date-publication [2013/04/01-Present].

The search was modified with respect to the location and the start date depending on the outbreak under consideration. Thus for the Jeddah outbreak, [Al-Hasa OR Al-Ahsa] was replaced by [Jeddah] and the Date-publication was changed to [2014/01/01-Present], and for the Riyadh 2014 and 2015 outbreaks, [Al-Hasa OR Al-Ahsa] was replaced by [Riyadh] and the Date-publication was changed to [2014/03/29-Present], covering both Riyadh outbreaks. Searches excluded articles with the following exclusion criteria, adapted from Xing et al. [5]: (1) The main study objective was not MERS-CoV; (2) The data analysed in the study were not collected from the relevant outbreak(s), for example for outbreaks in other countries or different outbreaks in Saudi Arabia, or it was unclear from which outbreak the data had been gathered, as no dates were given; (3) The data analysed in the study were related to a subject other than epidemiology of the relevant outbreak(s), such as feasibility studies for proposed therapies, animal studies on viral effects; (4) The article was not an original study, for example a review or a letter; (5) The study was carried out using only qualitative methodology; (6) The study sample size was <3 cases.

Further searches were carried out using the Web of Science Core Collection, in order to collect any relevant articles not detected in MEDLINE searches. The search equation used for the Al-Hasa outbreak was: Title: [Middle East Respiratory Syndrome coronavirus OR MERS-CoV] AND Topic: [Al-Hasa OR Al-Ahsa]. The search was refined to include only references from 2013 to the present, in English, in the categories Public Environmental & Occupational Health and Infectious Diseases. For the other outbreaks, [Al-Hasa] was changed to [Jeddah] or [Riyadh] accordingly, and the start date changed to 2014 or 2015 as appropriate.

In order to compare the timeline for publication dates in academic research journals to publication of public health bulletins, we also searched public health bulletins for any relevant outbreaks from the start of the earliest outbreak (Al-Hasa, 01/04/2014) to the present. We searched Morbidity and Mortality Weekly Report (MMWR) from the Centers for Disease Control and Prevention (CDC), and the World Health Organization (WHO) Weekly Epidemiological Report (WER) and monthly Bulletin of the World Health Organization. At the time of the literature review and spanning the time of the MERS-CoV outbreaks, the Saudi Epidemiology Bulletin was inaccessible for the relevant time period, with issues only available online up to 2012 [http://ftp.epu.sa/Bulletin.html, accessed 31.08.2016].

Data analysed

Articles were classified as in Xing et al. [5] according to four categories (1) investigation and surveillance; (2) case management; (3)
prevention and control; and (4) psychobehavioural aspects. Details for each study were recorded in a data-collection grid including authors, study title and journal, volume and date of publication, study design and type, domain, setting, and study characteristics, such as sample size (initial and final if applicable for study design), case definition criteria, location of patient recruitment and type of data collection. We also recorded where possible statistical analyses information, and data quality assurance processes, such as use of double-data entry, double blinding, or checking data for errors, if described in material and methods section.

Publication timeline and MERS-CoV study citations

We determined the timeline for publication and citation of retained articles, where submission, acceptance and publication dates were known. Submission and acceptance dates were derived from the journals or MEDLINE records, while publication date was taken as when the article was first became available in full text format; when both a print and an online publication dates were available, the publication date was taken as the earlier of the two. If only a publication month was available, the date was assumed to be the 15th of the month. Number of citations for an article on a particular outbreak was based on the Web of Science (Thomas Reuters) record on 7th September 2016 (https://apps.webofknowledge.com/). The impact factor of the journal in which each retained article was published was noted from the Journal of Citation Reports database for 2015 (Thomas Reuters). The impact factors for articles published within one year of the relevant outbreak were compared to the impact factors for articles published thereafter. To provide a control sample of articles, the submission-to-acceptance and acceptance-to-publication sequences and the citation number within six months and thereafter was also recorded for two articles within the same journal issue as each MERS-CoV article being analysed. This would allow us to determine if the MERS-CoV articles were cited more frequently than articles on other subjects published in the same journal issues. In each case, we selected control articles that either immediately preceded or immediately followed the relevant MERS-CoV article. The selection depended on the pagination in the particular journal issue. For example, if the MERS-CoV article was the first article in an issue, we chose the two following articles (of the same type) as the controls, but if it was the last article we picked the two preceding articles (of the same type) as controls. If the MERS-CoV article was somewhere in the middle, we picked the article immediately before and the article immediately after as controls.

Statistical analyses

Data were analyzed using Excel (Microsoft Corporation, Redmond, WA, USA) with Real Statistics add-ins (http://www.real-statistics.com/) and/or Social Science Statistics (http://www.socscistatistics.com/Default.aspx). Kruskal–Wallis analysis was carried out to compare medians for submission-acceptance and acceptance-publication times and numbers of citations between MERS-CoV and control articles and for the articles submitted during any of the four outbreaks to all other articles for which data was available for journal impact factors, numbers of citations and time period between submissions to publication. A \( p \leq 0.05 \) was taken as significant. Kaplan–Meier curves were generated and log-rank test analyses were carried out to compare proportions of MERS-CoV versus control articles under review (submission-acceptance) or under publication (acceptance-publication) for time periods from 0 to 400 days. A \( p \leq 0.05 \) was accepted as significant.

### Table 1

| Outbreak(s)          | Number of articles |
|----------------------|--------------------|
| Al-Hasa only         | 23                 |
| Al-Hasa + Jeddah     | 2                  |
| Al-Hasa + Jeddah + Riyadh 2014 | 3                  |
| Al-Hasa + Riyadh 2014 | 1                  |
| Jeddah only          | 13                 |
| Jeddah + Riyadh 2014 | 5                  |
| Jeddah + Riyadh 2015 | 1                  |
| Jeddah + Riyadh 2014 and 2015 | 1                  |
| Riyadh 2014 only     | 12                 |
| Riyadh 2015 only     | 4                  |
| All outbreaks        | 3                  |
| **Total**            | **68**             |

### Table 2

| Outbreak          | Number of article |
|-------------------|-------------------|
|                   | Alone | Combination | Total |
| Al-Hasa           | 23    | 9            | 32    |
| Jeddah            | 13    | 15           | 28    |
| Riyadh 2014       | 12    | 13           | 25    |
| Riyadh 2015       | 4     | 5            | 9     |
| **Total**         | 52    | 42           | 94    |

Total of 94 arises from the sum of articles considering each outbreak alone and in combination with other outbreak(s); thus few of the 68 articles (Table 1) are counted more than once.

### Results

#### Literature review

The initial MEDLINE searches produced 543 articles for Al-Hasa, 451 articles for Jeddah, and 451 articles for Riyadh. Most articles were retrieved in more than one of the searches, and in some cases an article retrieved in a particular search proved to be more relevant to another outbreak. For the Web of Science searches, there were 399 articles for Al-Hasa, 302 for Jeddah and 299 for Riyadh. There was substantial overlap with the MEDLINE results. Fig. 1 shows a flow diagram for selection of the final 68 unique articles after exclusion criteria were applied and articles were combined from MEDLINE and Web of Science searches [11–17, 19–79]. When these 68 articles (Supplementary Appendix 1) were assigned to the most relevant outbreak, sixteen of the 68 articles were common to two, three or all outbreaks, covering for example evolutionary analyses in which sequences of viruses from more than one of the outbreaks were used, or epidemiology of the whole country (Table 1). The final result, when these sixteen articles were distributed, was that the Al-Hasa outbreak featured in 32 articles, either alone or in combination with other outbreaks, the Jeddah outbreak in 28 articles, the Riyadh 2014 outbreak in 25 articles and the Riyadh 2015 outbreak in nine articles (Tables 1 and 2).

The public health bulletins searches of MMWR, WER and the monthly Bulletin of the WHO revealed few articles specific to any of the outbreaks and none were published during the relevant outbreaks. In MMWR, a search of ‘Middle East Respiratory Syndrome coronavirus OR MERS-CoV’ covering from the start of the Al-Hasa outbreak (April 1st 2013) to the present uncovered seven articles, in which two (June 14th 2013 and September 27th 2013) specifically mentioned the Al-Hasa outbreak while one (February 19th 2016) specifically mentioned the Riyadh 2015 outbreak. Five records in the WER for the same time period referenced MERS-CoV, but were not specific to the relevant outbreaks. The articles focused for example on prevention and control guidelines, including travel advice for Hajj pilgrims. In the same period, the Bulletin of the World
Health Organization included six MERS-CoV articles, including Public Health Round-ups, and an article on pilgrims returning from Hajj, and an article on steps that should be taken regarding surveillance, awareness raising and diagnostic testing capacity, but none specific to any of the outbreaks in this review. The Ministry of Health for Kingdom of Saudi Arabia portal provides daily reports on new cases as they arise, including the cases in the relevant outbreaks [http://www.moh.gov.sa/].

Study characteristics

The articles were divided into four categories, which could be further divided into research domains, as shown in Table 3. Where an article contained elements of more than one category, it was categorised into the category that dominated the subject matter of the article. Supplementary Appendix 1 shows the categorisation of each of the 68 final articles according to study characteristics. The majority of articles were in the ‘Investigation and surveillance’ category (57.4%), with 33.8% of articles mainly concerned with aspects of viral transmission. And 29.4% of the articles were in the ‘Case management’ category, 10.3% in ‘Prevention and control’ and 2.9% in ‘Psychobehavior’ (Table 3).

In terms of the study types, they were either descriptive epidemiology (60.3%) or analytic epidemiology (39.7%) (studies to quantify the association between exposures and outcomes and/or establish causal relationships). Studies were retrospective cohort studies (52.9%), prospective cohort studies (11.8%) or descriptive (longitudinal) cohort studies (14.7%) (Supplementary Appendix 1). The remainder studies were mathematical modelling studies (16.2%) or case control-studies (4.4%). The majority of recruitment occurred in hospitals/primary healthcare centres (76.5%), the community (7.4%), laboratory (5.9%) or college (1.5%), with 8.8% not specified/applicable. In most cases, data was used that was initially collected for other purposes, in particular hospital, medical or exposure records (58.8%; including three where biological specimens were also collected and one where interviews were also performed) or secondary data re-analysis from other studies (5.9%), while the remainder was from biological specimen collection (16.2%), questionnaires (8.8%), sequence data (5.9%; including two where biological specimens were also collected), or was not specified (4.4%). In most studies, MERS-CoV was confirmed by means of PCR (75%), as recommended by the CDC and WHO, sometimes in combination with clinical signs and once with western blotting (Supplementary Appendix 1). Presence of anti-MERS-CoV

![Flow diagram for article selection process.](image)
protein antibodies was included in three studies (4.4%). Nine studies (13.2%) included awareness, emotional responses or guidelines arising from an outbreak, and in five studies it was not specified (7.4%) (Supplementary Appendix 1). Sample size was reported in 61 studies (89.7%), with a median of 105 cases. In studies with no sample size, the studies were revision of infection prevention and control standards or correlation of online reports with reported cases (Supplementary Appendix 1).

In terms of data quality assurance/control, there were few studies that specified which processes were applied. In six studies, there was some form of double-data entry and/or double-blinding, while in eight studies there was some element of checking data for errors (Supplementary Appendix 1).

**Journals publishing MERS-CoV articles**

The 68 selected articles were published in 40 different journals. Some journals published more than one article. Seven articles were published in *Emerging Infectious Diseases* (10.3%) and six in the *International Journal of Infectious Diseases* (8.8%), four each were published in *Lancet Infectious Diseases* and in *Clinical Infectious Diseases* (5.9% each) and three (4.4%) each in the *American Journal of Roentgenology*, *Eurosurveillance* and *mBio*. Two (2.9%) were published in each of *Epidemics*, *Lancet, New England Journal of Medicine* and *PloS Current Outbreaks*. The median impact factor for the 40 journals publishing the 68 retained articles was 3.44 (Interquartile range (IQR) 5.88).

**Publication timeline**

When dates were available, we derived the publication timelines for the retained articles for each of the four outbreaks. Fig. 2 shows the cumulative percentages of articles submitted, published and accepted for each outbreak, from the beginning of the relevant outbreak to the present, Fig. 2A: Al-Hasa (21 articles), Fig. 2B: Jeddah (17 articles), Fig. 2C: Riyadh 2014 (14 articles), Fig. 2D: Riyadh 2015 (7 articles). The timing of the outbreak is indicated on each graph to illustrate that submission, acceptance and publication of the majority of articles occurred after the outbreaks. One of the retained articles was submitted during the Al-Hasa outbreak and published within a month [41], two were submitted and one accepted during the Jeddah outbreak [19,45], one was submitted for the Riyadh 2014 outbreak [78], and two articles were submitted and one accepted during the Riyadh 2015 outbreak [44,51] (Fig. 2). This left insufficient numbers of articles to compare impact factors, submission timelines and numbers of citations for articles submitted, accepted or published during any particular outbreak to those submitted, accepted or published after the same outbreak.

**MERS CoV article characteristics compared to control articles**

We determined if there were any differences in timelines from submission-to-acceptance or acceptance-to-publication, or number of article citations, for articles published on any of the MERS-CoV outbreaks compared to control articles on other subjects in the same journal issue. Fig. 3 shows Kaplan–Meier curves representing the proportion of articles under submission/review (Fig. 3A), and the proportion of articles under publication (accepted) for time periods from 0 to 400 days for MERS-CoV versus control articles (Fig. 3B). Log-rank analyses showed no significant difference in hazard rates for submission-to-acceptance (*z* = 0.45, *p* = 0.65) or acceptance-to-publication (*z* = 1.3, *p* = 0.19) for MERS-CoV versus control articles. There was no statistical difference in the median time of submission-acceptance for MERS-CoV articles and control articles (median 57.5 vs. 83.5 days) (*p* = 0.065). Likewise, there was no significant difference between the median acceptance-publication times for MERS-CoV versus control articles (medians 34.5 and 43 days respectively; *p* = 0.132). However, the median citation
Discussion

Immediate and reliable collection, analysis and dissemination of epidemiological information during infectious disease outbreaks are critical for filling in the knowledge gaps [2–4]. The primary method for communicating research findings in the medical and scientific community is via journal articles [5]. However, the results of our study show that the majority of publications on epidemiology of MERS-CoV outbreaks in Al-Hasa, Jeddah and Riyadh occurred after the outbreaks had ended. Submission-to-acceptance or acceptance-to-publication times were not significantly different for articles on MERS-CoV outbreak epidemiology compared to control articles. Articles that were eventually published were dominated by descriptive epidemiology and were mainly in the investigation and surveillance domain. Most epidemiology articles on MERS-CoV were published with no preferential advantage over other articles indicating non-expedited review and publication time.

There are various factors that contribute to delayed publication of articles, including author-related and journal-related factors [5]. Input from the epidemiological research community and the scientific publishing industry would be important to facilitate timely publication of emerging infectious diseases. Author-related factors that can result in submission and publication delays include: the time needed to prepare and disseminate protocols, questionnaires and surveys, as well as to prepare the publication for initial submission, choose an appropriate journal, and prepare further submissions necessitated by rejection by the first-choice journal [5]. Publisher-related delays can relate to identification of appropriate reviewers, waiting for reviews, deciding on whether to publish on the basis of the reviews and technical aspects of journal preparation [5]. Publication likelihood can be influenced by factors including geographical location of the researchers, study domain, the disease under consideration, the novelty of the study and positive or negative results [80,81].

It is important to ensure the quality of studies by a robust peer-review process. However, there are developments in the medical and scientific publishing industry that may help in expediting the process of article publication in future emerging infectious dis-
eases. It is important to minimise the delay between generating and publishing research, by streamlining peer-review process, and targeting specific research audiences. It is also important to offer fast-track and rapid publication options, particularly to advanced online publication. Publication costs and fees can be a barrier to researchers, particularly in developing countries. For epidemiology research, standardization of protocols and questionnaires, and greater accessibility of real-time online information systems, would be of assistance to researchers for rapid collection, analysis and dissemination of research. The need for better data management was identified as an issue in the recent Ebola outbreak [82]. An example of this need is in terms of improved data harmonization and access to application tools. Standardization of protocols would assist in timely production of epidemiological studies. The European Centre for Disease Prevention and Control (ECDC) has published a comprehensive handbook on methods and applications in monitoring of data quality and evaluation of surveillance systems [83,84].

Other means of communication of information on outbreak epidemiology and other aspects of emergent infectious diseases may include social media networks among healthcare professionals [85]. Access to online resources and internet-based participatory surveillance system such as HealthMap could be useful in detection and monitoring outbreaks [17,18]. However, presentation of epidemiological information that has been collected and analysed by recognised, sound epidemiological methods and subjected to peer-review in appropriate journals remains a vital means for reliable communication within the medical/scientific community. Current indications are that MERS-CoV has limited epidemic potential [85,86]. However, human-to-human transmission occur usually in healthcare-associated outbreaks such as those included in the current review, and other outbreaks from other countries in the Middle East, and the Republic of Korea [11–14,22–27]. The healthcare associated outbreaks were linked to poor compliance with infection prevention and control procedures [53,64,87–91]. Effectiveness of consistent promotion and application of basic and advanced infection control procedures in reduction of cases has been demonstrated in hospital-associated MERS-CoV outbreaks in Saudi Arabia and Korea [53,85,91]. However, MERS-CoV has a high morbidity and case-fatality rate, particularly among ICU and/or critically ill patients, those with comorbid illness, older patients and those with a high viral load [11,12,15,92–94]. The potential for viral mutations, for example in the viral spike (S) protein, which mediates viral entry into host cells, or in viral proteases such as Mpro, could increase viral affinity for human host cells and expand host cell range [50,94–96]. Thus, surveillance, contact tracing and research into possible animal hosts and transmission pathways to humans need to be prioritized [37]. This is vital to fill in gaps in knowledge and understanding of MERS-CoV. Such gaps include exposure to infected dromedary camels, direction of transmission between humans and camels, the role of a third link in the chain of cross-species transmission, such as bats, and the reasons behind limited human-to-human transmission [97]. There is no specific therapy for MERS-CoV, despite promising results in animal studies for few antiviral synthetic peptides and candidate vaccines. GLS-5300, a DNA-plasmid vaccine encoding MERS-CoV S protein (Inovio, GeneOne Life Science Inc. and the Walter Reed Army Institute of Research) is the first potential MERS-CoV vaccine to enter human testing [98], however it is intended for prophylactic use, rather than in outbreak situations. In terms of diagnosis, MERS-CoV was confirmed by PCR. This is expected, as real-time PCR is the major method for detection of MERS-CoV [99]. Antibody-based methods are not widely used as yet, although there is some interest in developing and implementing such methods in routine testing, especially to test for possible previous infection or if symptoms arose more than fourteen days previously as recommended by the Centers for Disease Control and Prevention (CDC) [99,100].

In conclusion, most epidemiology articles on MERS-CoV had no preferential publication advantage over other articles. Collaboration of the research community and the scientific publishing industry is needed to facilitate timely publication of emerging infectious diseases.

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**Competing interest**

None declared.

**Ethical approval**

Not required.

**Appendix A. Supplementary data**

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijjit.2017.05.005.

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