Adapting to the global shortage of cholera vaccines: targeted single dose cholera vaccine in response to an outbreak in South Sudan

Lucy A Parker, John Rumunu, Christine Jamet, Yona Kenyi, Richard Laku Lino, Joseph F Wamala, Allan M Mpairwe, Iza Ciglenecki, Francisco J Luquero, Andrew S Azman, Jean-Clement Cabrol

Shortages of vaccines for epidemic diseases, such as cholera, meningitis, and yellow fever, have become common over the past decade, hampering efforts to control outbreaks through mass reactive vaccination campaigns. Additionally, various epidemiological, political, and logistical challenges, which are poorly documented in the literature, often lead to delays in reactive campaigns, ultimately reducing the effect of vaccination. In June 2015, a cholera outbreak occurred in Juba, South Sudan, and because of the global shortage of oral cholera vaccine, authorities were unable to secure sufficient doses to vaccinate the entire at-risk population—approximately 1 million people. In this Personal View, we document the first public health use of a reduced, single-dose regimen of oral cholera vaccine, and show the details of the decision-making process and timeline. We also make recommendations to help improve reactive vaccination campaigns against cholera, and discuss the importance of new and flexible context-specific dose regimens and vaccination strategies.

Lancet Infect Dis 2017

Published Online
January 18, 2017
http://dx.doi.org/10.1016/S1473-3099(16)30472-8

Médecins Sans Frontières, Geneva, Switzerland (L A Parker PhD, C Jamet MPH, I Ciglenecki MD, A S Azman PhD, J-C Cabrol MD)**; Department of Public Health, Universidad Miguel Hernández, Alicante, Spain** (L A Parker)**; CIBER Epidemiología y Salud Pública, Madrid, Spain** (L A Parker)**; Ministry of Health, Juba, South Sudan** (J Rumunu MPH, Y Kenyi Dip, R L Lino MSc)**; World Health Organization, Juba, South Sudan** (J F Wamala MPH, A M Mpairwe MPH)**; Epicentre, Paris, France** (F J Luquero PhD)**; Department of International Health** (F J Luquero)**, and Department of Epidemiology** (A S Azman)**, Johns Hopkins University, Baltimore, Maryland, USA**

Correspondence to:
Dr Iza Ciglenecki, Médecins Sans Frontières, 1202 Geneva, Switzerland
iza.ciglenecki@geneva.msf.org

Vaccine stockpile and supply limitations

Recent large, protracted cholera epidemics in the Caribbean and Africa (such as those in 2008, 2010, and 2012) highlight the limitations of classic outbreak response strategies that, in addition to case management, focus mainly on the promotion of handwashing, improved sanitation, and use of safe water.[1–3] Oral cholera vaccines have emerged as an effective new tool, bringing hope for improved cholera prevention and control both in endemic and epidemic settings. Three oral cholera vaccines are prequalified by WHO: Dukoral (Valneva, Lyon, France), Shanchol (Shantha Biotechnics Ltd, Hyderabad, India), and Euvichol (Eubiologics, Gangwon-do, South Korea). All three are licensed as a two-dose regimen and are safe and effective.[4–6] Although oral cholera vaccines have also proven feasible and effective as an outbreak control measure,[7–9] wider reactive use is hindered by a series of obstacles: delays in identifying and confirming initial cases and declaring outbreaks, the rapid and dynamic evolution of outbreaks, a recommended two-dose vaccine regimen, and above all, the global shortage of oral cholera vaccines.

In 2013, a global stockpile of oral cholera vaccines, initially of 2 million doses per year, was created to ensure vaccine availability for outbreak control.[10] Shanchol was the vaccine chosen for the stockpile because it was lower in price, it was easier to administer, and had potentially larger manufacturing capacity. The GAVI Alliance later committed to fund up to 70 million doses from 2014 to 2018, to expand outbreak and other emergency vaccination campaigns, and dedicated the remaining doses to cholera control in endemic countries. However, production and supply of Shanchol is behind schedule: only 4 million doses of the vaccine were available for purchase in 2014–15. Because of this shortage nearly all of the vaccine produced immediately goes to the emergency stockpile, which is the only way to access Shanchol, including for outbreak control in endemic countries. Furthermore, to align with the scale of global vaccine availability, requests for oral cholera vaccines have been substantially smaller than the true demand, hindering efforts to forecast future demand. Fortunately, additional doses of the newly prequalified Euvichol have become available this year, helping to alleviate some of this shortfall.

The stockpile is managed by the International Coordination Group under the WHO secretariat, comprised of representatives from Médecins Sans Frontières, International Federation of the Red Cross, UNICEF, and WHO. Countries or agencies wishing to use oral cholera vaccines in response to outbreaks must submit a request to the International Coordination Group including information about laboratory confirmation of cholera cases, a risk assessment of the probability of epidemic expansion, an overview of the country's capacity to control the outbreak, a detailed vaccination plan with a map of targeted areas, a plan to cover the operational costs of vaccination, and an outline of the monitoring and evaluation activities used to learn from each deployment.[11] This process, meant to direct scarce supplies of vaccine to where they could have most effect, in practice presents substantial hurdles to rapid use of oral cholera vaccines in emergencies, especially in rapidly evolving epidemics.

The 2015 cholera epidemic in Juba, South Sudan

These obstacles were highlighted in June 2015, when cholera broke out in Juba, the capital of South Sudan (figure 1). Juba is a city estimated to have between 500 000 and 1 million inhabitants, with massive population movements both into and out of the city because of civil strife that started in December 2013.

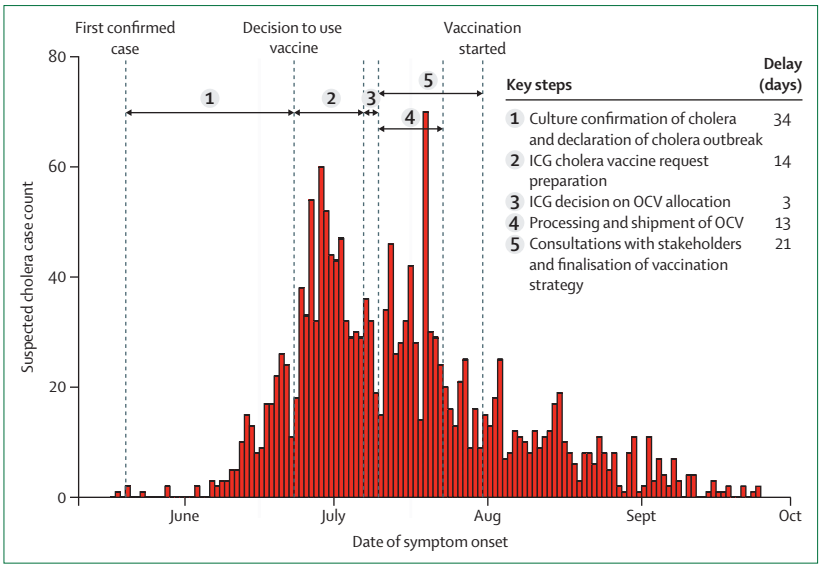

Figure 1: **Epidemic curve and key time delays in vaccination process in Juba, South Sudan, 2015**
Suspected cases shown in bars, and defined as all individuals with acute watery diarrhoea regardless of dehydration status and age. Cholera cases were captured in Juba by a standardised national line list, which was used in all centres treating patients with cholera, including cholera treatment centres and oral rehydration points throughout the city. ICG=International Coordination Group. OCV=oral cholera vaccine.

The cholera outbreak spread rapidly in several disjointed neighbourhoods of Juba, with over 100 suspected cases reported at health facilities within a month of the first culture-confirmed case. Historical data from South Sudan,[12] including those from the 2014 outbreak, suggested that Juba could serve as a hub of transmission to the whole country, which has experienced epidemics lasting as long as 8 months. To rapidly curb the 2015 epidemic, decrease mortality, and reduce the chance of spread to other parts of the country—particularly those in the middle of civil war—the National Cholera Task Force proposed use of oral cholera vaccines alongside improvements in case management, access to safe water, and sanitation and hygiene promotion.

Preparations for the International Coordination Group request began the week the outbreak was declared (figure 1). With fewer than 900 000 doses in the oral cholera vaccine stockpile and rough population estimates of up to 1 million people in Juba alone, the decision of how to best use the limited vaccine available was complex. The evidence available suggested that the first dose of Shanchol is highly immunogenic, and that on its own it probably provides some clinical protection (33–67% for estimates for the period 6–22 months after vaccination), although at a lower level than the full two-dose regimen (40–87% for estimates for the period 6–24 months after vaccination).[5,7,9,13–16] However, providing just one dose per person would allow double the number of people to be vaccinated, and could potentially increase population-wide protection (herd immunity), thereby having a greater effect on public health.[17]

On the basis of this information, alongside promising initial results from a large single-dose clinical trial[15] presented in a scientific meeting at the time of the outbreak, the decision was taken to target a larger at-risk population with a single dose of oral cholera vaccine (Shanchol). After wider consultations with key stakeholders, the Ministry of Health, supported by Médecins Sans Frontières, requested 640 000 doses to cover Juba and Torit counties. Torit county had no reported cases at the time, but is thought of as an area with substantial history of cholera prevalence and typically high case-fatality ratios.[18,19] The request was submitted 14 days after the epidemic was first declared (figure 1). The International Coordination Group reviewed the request within days, but approved only 270 340 doses for a two-dose schedule in Torit, because they judged the epidemic in Juba too mature for use of oral cholera vaccines. However, since the number of new cases did not decrease in Juba and no cases had been reported in Torit, another round of discussions re-assessed how to best use the number of doses approved, which was insufficient to cover the whole of Juba city, even with a single-dose strategy. The fact that only selected areas within a large urban population would receive the vaccine, while other areas would not, led to fears of civil unrest due to high demand for the vaccine in non-targeted areas. The Ministry of Health maintained the focus on Juba to maximise the effect on public health by targeting areas of the city with sustained or increasing disease transmission (on the basis of Ministry of Health situation reports[12] and analyses of the line list data), and high-risk groups (eg, prisoners, internally displaced people, and health-care workers). It took 3 weeks from the International Coordination Group decision to the time when all stakeholders, from national to local levels, supported a revised, targeted, single-dose vaccination campaign—the point at which the first people could be vaccinated (figure 1).

The oral cholera vaccines campaign

The targeted areas were defined conservatively because of concern about running out of vaccines (figure 2). Social mobilisation was also deliberately limited to avoid people from non-targeted areas coming to vaccination sites. Ultimately, 140 249 doses were administered in targeted areas of Juba during 6 days of a mass vaccination campaign, and by mobile teams targeting the high-risk groups in subsequent days. The vaccine was primarily delivered through fixed vaccination posts (red dots, figure 2) and temporary mobile vaccination sites that were active for 1–2 days each after the number of individuals coming to the fixed posts declined (green dots, figure 2). The feared civil unrest or massive demand for the vaccine did not materialise. The remaining doses were used as part of a comprehensive targeted intervention with water and

sanitation and hygiene promotion in the neighbourhoods with cases in Juba (22 128 doses, sites identified by blue dots, figure 2), and to protect internally displaced people outside of Juba in areas with on-going fighting and recent population movements (107 963 doses to the large UN Protection of Civilian camps in Bentiu and Malakal).

Lessons learned

This experience highlights many of the difficulties in planning effective and timely reactive oral cholera vaccine campaigns. It took over a month to culture-confirm the initial cases and declare the outbreak, the first requirement before a request for vaccines can be submitted (figure 1). For a timely response to epidemics, countries should improve laboratory and surveillance capacity, and rapidly declare cholera outbreaks. The complex process of gathering and analysing data, to decide on whether oral cholera vaccines would be effective and to complete the vaccine request to the International Coordination Group, was further complicated in this case by consultations with all stakeholders because of the use of an alternative vaccination strategy. This experience illustrates the need for guidance on how and when to use oral cholera vaccines reactively, and for simplifying the mechanisms to access oral cholera vaccines from the stockpile to allow for timely use of vaccine in response to outbreaks, particularly in the most vulnerable settings with weak data collection systems.

Clear data-driven guidance on when and where a vaccine should be used reactively is available for other stockpiled vaccines, such as meningitis,[20] but it does not currently exist for oral cholera vaccine (panel). By reviewing historical outbreak dynamics and response timelines, WHO and the Global Taskforce for Cholera Control should consider creating clear recommendations for the reactive use of oral cholera vaccines. With this guidance, countries can update their cholera response plans to include a framework for use of reactive vaccination, which can reduce the time needed to make decisions within each country during epidemics.

Simplifications to the International Coordination Group application and process could also reduce delays in reactive oral cholera vaccine campaigns. This application requires that countries submit detailed plans about how the vaccine will be distributed. Although this is crucial for a successful campaign, these details are often made just before vaccination to adapt to the changing epidemiological situation. Eliminating these requirements and providing more autonomy to the Ministries of Health to make rational, context-tailored decisions, can reduce unnecessary delays. In high-risk settings experiencing frequent cholera epidemics, such as South Sudan, the International Coordination Group could include a mechanism for conditional pre-approval of oral cholera

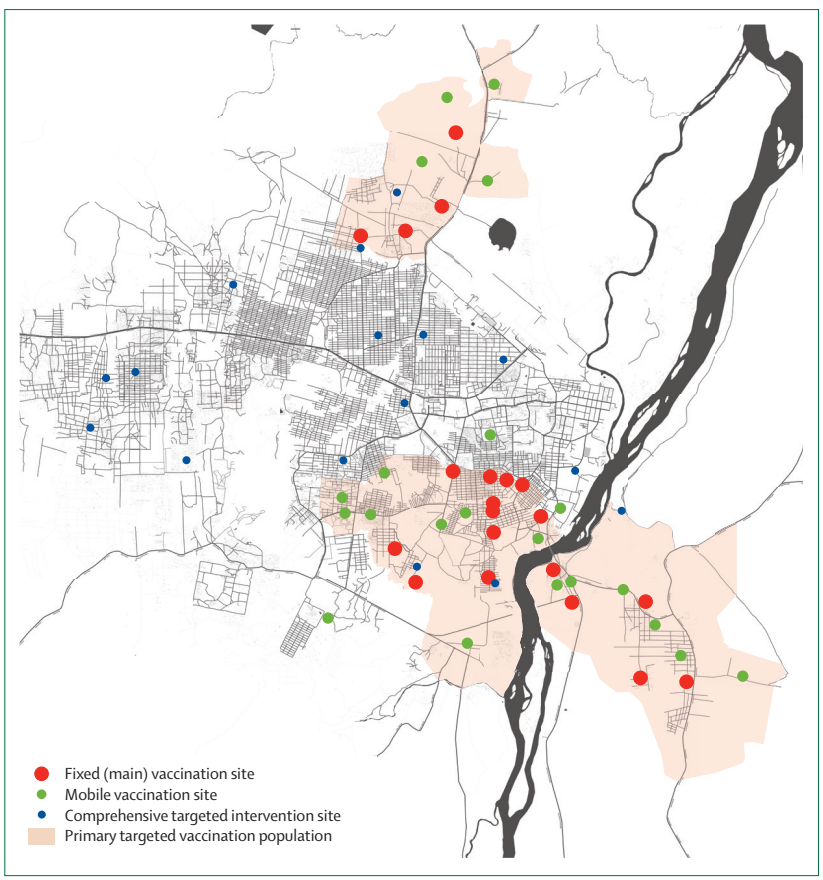

Figure 2: **Vaccination areas targeted in a mass vaccination campaign in Juba, South Sudan**
Vaccination areas (orange shading) and locations of vaccination posts (red, green, blue dots). Red dots indicate the fixed vaccination posts, green dots represent mobile sites that were active for 1–2 days each. Blue dots represent vaccination sites set up in response to confirmed cases (comprehensive targeted intervention), which provided the vaccine to approximately 22 000 individuals as a single dose.

Panel: **Key recommendations to improve the timeliness and effectiveness of reactive cholera vaccination**

- Improve in-country laboratory and surveillance capacity in cholera-prone settings to facilitate rapid declaration of outbreaks
- Develop a data-based framework for assessing the need and potential effect of reactive oral cholera vaccine campaigns
- In high-risk countries, incorporate reactive vaccination plans with national cholera control plans
- Simplify the International Coordination Group request process (eg, by removing requirements for detailed planning documents)
- Consider the creation of pre-approval mechanism to let the International Coordination Group pre-validate the country's capacity for vaccination and historical epidemiology and risk profile
- Consider the creation of national or regional oral cholera vaccine stockpiles in cholera-prone areas to permit rapid response
- Develop clear and transparent criteria to guide the prioritisation of vaccines among competing requests
- Continue to increase supply of oral cholera vaccine

vaccines (evaluating details of the context, risk factors, local capacity for response, and cold chain), thereby allowing countries to make a rapid request via a shortened skeleton request form if or when an outbreak is confirmed. As global vaccine supply constraints ease, high-risk countries (or regions) could also consider stockpiling their own vaccine for rapid use.

The shortage of vaccines also means that the International Coordination Group must prioritise among competing demands. At the time of South Sudan's request to the International Coordination Group, an epidemic was raging among Burundian refugees in Tanzania,[21] large cholera endemic areas in Nepal were at increased risk because of displacement following the earthquake,[22] and Haiti had a resurgence of cholera in several locations. There are no clear criteria to guide International Coordination Group members on how to make allocation decisions with competing emergencies. Such criteria are urgently needed, to allow for realistic planning and to avoid delays that can compromise the timely and effective response to epidemics.

It is essential to address the shortage of vaccines, which is at the core of these problems and represents the greatest threat to their effective use. The manufacturer of Shanchol must keep its commitments to the global health community and make faster progress in increasing production, and other emerging manufacturers should be supported to hasten WHO prequalification. Fortunately, since this epidemic, a new manufacturer of prequalified oral cholera vaccines has met some of the demand, although we continue to face supply limitations, as illustrated by the 2016 oral cholera vaccine deployment to Haiti in response to Hurricane Matthew.[23]

Flexible alternative vaccination strategies are needed, including highly targeted vaccination campaigns and single-dose regimens, to help to cope with global vaccine supply limitations and in challenging humanitarian contexts, including those with highly mobile populations. Clinical trial results from Bangladesh that show the efficacy of single-dose oral cholera vaccine at an individual level,[12] together with the experiences from South Sudan,[24] should help to accelerate decision-making. Although more evidence is needed on the effectiveness and impact of alternative strategies, WHO and manufacturers should make clear recommendations about how to move forward with off-label uses of the vaccine when supply shortages or logistical constraints make the standard strategies impossible.

As illustrated in South Sudan, use of oral cholera vaccine, in response to an outbreak can be complex, with delays caused by multiple factors. By critically revisiting reactive vaccination experiences, we can better understand the delays and adapt to improve future responses. By focusing on improved diagnostic capacity and planning at the country level, providing a clear framework for reactive vaccination decision making, simplifying the processes for gaining access to the global stockpile, and ensuring adequate production of oral cholera vaccines, future campaigns could avert more cases and save more lives.

Contributors

LAP, IC, FJL, and ASA wrote the first draft of the manuscript. JR, CJ, IC, FJL, ASA, and J-CC conceived the operational strategy and prepared the International Coordination Group application. LAP, JR, RLL, JFW, AMM, and IC discussed and approved the vaccination plan in Juba. LAP, JR, YK, and IC oversaw the implementation of the campaign. All authors read, critically revised, and approved the manuscript. IC had full access to all the data and final responsibility for the decision to submit the paper for publication.

Declaration of interests

We declare no competing interests.

Acknowledgments

We thank the teams in Juba and others involved in cholera response, and Patricia Kahn for her involvement in reviewing the manuscript. This paper describes operational activities that were funded by Médecins sans Frontières. No direct funding was assigned to the paper, and the decision to write and submit the manuscript was made by the authors alone.

References

1 Mintz ED, Guerrant RL. A lion in our village—the unconscionable tragedy of cholera in Africa. *N Engl J Med* 2009; **360:** 1060–3.

2 Abubakar A, Almiron M, Charito A, et al. Cholera, 2014. *Wkly Epidemiol Rec* 2015; **90:** 517–44.

3 Barzilay EJ, Schaad N, Magloire R, et al. Cholera surveillance during the Haiti epidemic–the first 2 years. *N Engl J Med* 2013; **368:** 599–609.

4 Bhattacharya SK, Sur D, Ali M, et al. 5 year efficacy of a bivalent killed whole-cell oral cholera vaccine in Kolkata, India: a cluster-randomised, double-blind, placebo-controlled trial. *Lancet Infect Dis* 2013; **13:** 1050–6.

5 Khatib AM, Ali M, Seidlein von L, et al. Effectiveness of an oral cholera vaccine in Zanzibar: findings from a mass vaccination campaign and observational cohort study. *Lancet Infect Dis* 2012; **12:** 837–44.

6 Desai SN, Pezzoli L, Martin S, et al. A second affordable oral cholera vaccine: implications for the global vaccine stockpile. *Lancet Glob Health* 2016; **4:** e223–24.

7 Luquero FJ, Grout L, Ciglenecki I, et al. Use of *Vibrio cholerae* vaccine in an outbreak in Guinea. *N Engl J Med* 2014; **370:** 2111–20.

8 Ciglenecki I, Sakoba K, Luquero FJ, et al. Feasibility of mass vaccination campaign with oral cholera vaccines in response to an outbreak in Guinea. *PLoS Med* 2013; **10:** e1001512.

9 Ivers LC, Hilaire IJ, Teng JE, et al. Effectiveness of reactive oral cholera vaccination in rural Haiti: a case-control study and bias-indicator analysis. *Lancet Glob Health* 2015; **3:** e162–68.

10 Martin S, Lopez AL, Bellos A, et al. Post-licensure deployment of oral cholera vaccines: a systematic review. *Bull World Health Org* 2014; **92:** 881–93.

11 World Health Organization. Oral cholera vaccine stockpile. 2013. http://www.who.int/cholera/vaccines/ocv_stockpile_2013/en/ (accessed Oct 3, 2015).

12 Charles RC, Hilaire IJ, Mayo-Smith LM, et al. Immunogenicity of a killed bivalent (O1 and O139) whole-cell oral cholera vaccine, Shanchol, in Haiti. *PLoS Negl Trop Dis* 2014; **8:** e2828.

13 Desai SN, Akalu Z, Teshome S, et al. A randomized, placebo-controlled trial evaluating safety and immunogenicity of the killed, bivalent, whole-cell oral cholera vaccine in Ethiopia. *Am J Trop Med Hyg* 2015; **93:** 527–33.

14 Qadri F, Wierzba TF, Ali M, et al. Efficacy of a single-dose, inactivated oral cholera vaccine in Bangladesh. *N Engl J Med* 2016; **374:** 1723–32.

15 Sur D, Lopez AL, Kanungo S, et al. Efficacy and safety of a modified killed-whole-cell oral cholera vaccine in India: an interim analysis of a cluster-randomised, double-blind, placebo-controlled trial. *Lancet* 2009; **374:** 1694–702.

16 Azman AS, Luquero FJ, Ciglenecki I, Grais RF, Sack DA, Lessler J. The impact of a one-dose versus two-dose oral cholera vaccine regimen in outbreak settings: a modeling study. *PLoS Med* 2015; **12:** e1001867.

17 Azman AS, Rumunu J, Abubakar A, et al. Population-level effect of cholera vaccine on displaced populations, South Sudan, 2014. *Emerg Infect Dis* 2016; **22:** 1067–70.

18 Abubakar A, Azman AS, Rumunu J, et al. The first use of the global oral cholera vaccine emergency stockpile: lessons from South Sudan. *Plos Med* 2015; **12:** e1001901.

19 World Health Organization. South Sudan cholera outbreak updates. http://www.who.int/hac/crises/ssd/sitreps/juba_cholera_outbreak/en/index1.html (accessed Sept 7, 2016).

20 WHO. Managing meningitis epidemics in Africa: a quick reference guide for health authorities and health-care workers. Geneva: World Health Organization, 2015.

21 Médecins sans Frontières. Tanzania: 130 000 refugees vaccinated against cholera in the overcrowded Nyarugusu camp. July 30, 2015. http://www.msf.org/article/tanzania-130000-refugees-vaccinated-against-cholera-overcrowded-nyarugusu-camp (accessed Dec 5, 2016).

22 Nelson EJ, Andrews JR, Maples S, Barry M, Clemens JD. Is a cholera outbreak preventable in post-earthquake Nepal? *PLoS Negl Trop Dis* 2015; **9:** e0003961.

23 NPR. Haiti launches largest-ever cholera vaccination campaign. Nov 8, 2016. http://www.npr.org/sections/goatsandsoda/2016/11/08/501155987/haiti-launches-largest-ever-emergency-cholera-vaccination-campaign or other (accessed Dec 6, 2016).

24 Azman AS, Parker LA, Rumunu J, et al. The effectiveness of one dose of oral cholera vaccine in response to an outbreak: a case-cohort study. *Lancet Glob Health* 2016; **4:** e856–63.